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January 10, 1973

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NEWS & FEATURES **From** NIH January 10, 1973

Research Advances

SCIENTISTS DETERMINE STRUCTURE OF HUMAN PARATHYROID HORMONE

Scientists at the National Heart and Lung Institute (NHLI), the Mayo Clinic, and the Ciba-Geigy Pharmaceutical Company have succeeded in determining the chemical structure and synthesizing the biologically active portion of human parathyroid hormone.

The results of these collaborative efforts reveal significant differences between the chemical structure of human parathyroid hormone and that derived from animal sources. They also make possible the first synthesis of sufficient quantities of the hormone's active component for experimental studies of its role in calcium metabolism and metabolic bone disease, for the development of diagnostic assay procedures for its measurement in human blood, and for clinical investigation of its potential use as a therapeutic agent in human disease.

Parathyroid hormone is biosynthesized and secreted into the bloodstream

(more)

Dr. H. Bryan Brewer, Jr., Head of the Section on Peptide Chemistry, Molecular Diseases Branch of the NIH National Heart and Lung Institute, places a sample of pure human parathyroid hormone in the Beckman Sequencer machine for sequential degradation of the hormone into its amino acid constituents. (NIH Photo #HL1)

Hormone (Cont'd)

by the four parathyroid glands which are located, in humans, in the neck behind the thyroid gland. The hormone is a protein which acts on the cells of bone, kidney, and intestinal tract to maintain a constant concentration of calcium in the blood. Removal of the gland causes a rapid decrease in blood calcium leading to serious neuromuscular abnormalities and death under certain circumstances.

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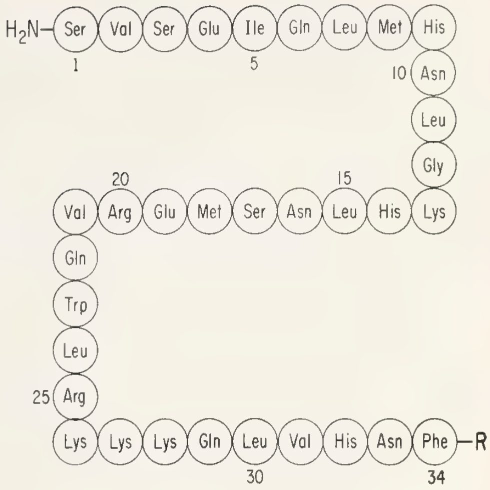

The sequence of 34 amino acid constituents of the biologically active portion of human parathyroid hormone is shown above. (NIH Photo #HL2)

Purified human parathyroid hormone is carefully measured out by NIH chemist Rosemary Ronan. Hormone for these studies was obtained from hundreds of frozen parathyroid gland tumors collected over the course of two years from 12 countries and supplied to NHLI by the Mayo Clinic in Minnesota. The total yield of hormone--a mere 3.8 milligrams--was sufficient for the determination of the structure of the hormone's biologically active fragment. (NIH Photo #HL3)

The NHLI researchers determined the amino acid sequence of the biologically active region of the hormone (the first 34 of the 84 amino acids comprising the molecule) using parathyroid glands collected by the Mayo Clinic team.

The scientists used the Edman technique to determine the sequence of the hormone. In this technique, one amino acid at a time is "cleaved" off the chain and identified by either gas chromatography or mass spectrometry. For this work they used a Beckman Sequencer, a machine that carves amino acids off the parent molecule at a rate of one amino acid every two hours.

This molecular "blueprint" was used by a research team at Ciba-Geigy, Ltd. in Basel, Switzerland, to synthesize the single chain molecular fragment by stringing together the constituent amino acids in the proper sequence.

Details of the chemical structure, including the precise sequence of the amino acids in the active portion of the human parathyroid hormone, were reported in the December 1972 issue of *Proceedings of the National Academy of Sciences* by Dr. H. Bryan Brewer, Jr., Dr. Thomas Fairwell, and Rosemary Ronan of NHLI; by Drs. Claude D. Arnaud and Glen W. Sizemore of the Mayo Medical School and Clinic.

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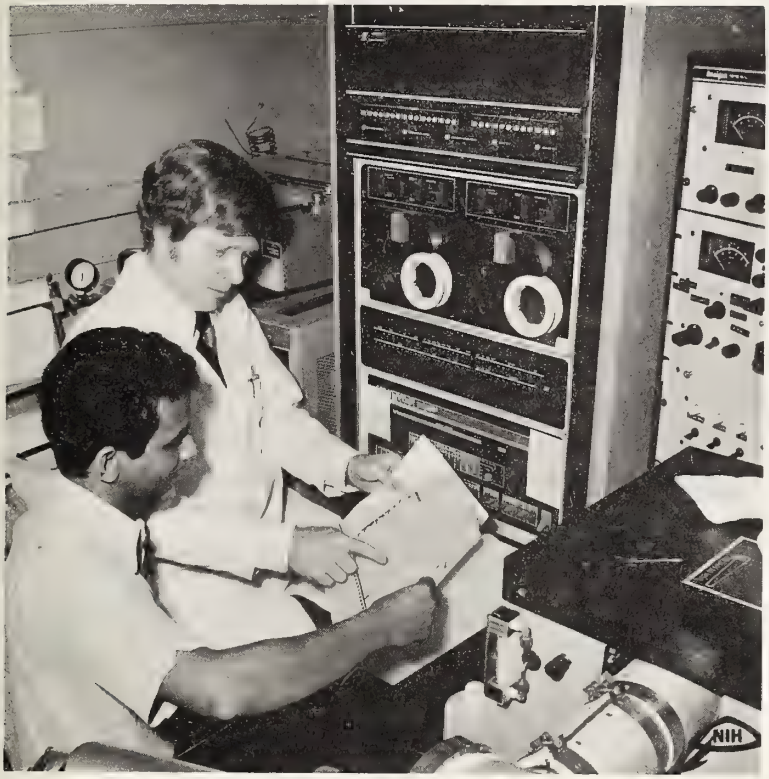
Hormone (Cont'd)



NHLI scientists used two analytical techniques to identify the amino acid constituents of human parathyroid hormone. In mass spectrometry, (left) an amino acid removed from the parent molecule is bombarded by electrons to produce a signal that identifies precisely the amino acid in question. Here, Dr. Thomas Fairwell and Dr. Brewer discuss the mass spectrum of one of the amino acids. (NIH Photo #HL4). In gas chromatography, (below) amino acids and other compounds are identified according to their varying solubilities in a thin coating of organic solvent. Here, NHLI chemist Ann Kelly and Dr. Brewer examine a gas chromatography strip chart used in the NHLI study. (NIH Photo #HL5)

#

Research Advances

FROZEN HUMAN MARROW CELLS RETAIN CAPACITY TO PRODUCE HEMOGLOBIN

Human bone marrow cells stored in the frozen state as long as nine months are able to function normally in the production of hemoglobin--the vital oxygen-carrying pigment of the blood. This finding by NIH-supported scientists brings closer the day when an individual's own previously frozen and stored marrow cells might be used to reconstitute his production of blood cells following lethal radiation or a catastrophic illness.

The capacity of such stored marrow cells to repopulate the marrow space has been demonstrated previously in rodents, dogs, and monkeys. However, the effectiveness of various freezing and storing techniques differs with species, and it has not always been possible to apply animal data to the situation in man.

Drs. John W. Adamson and Rainer Storb of the University of Washington School of Medicine and Veterans Administration Hospital, Seattle, carried out the present studies. They tested the viability of frozen stored human bone marrow cells by determining their capacity to synthesize hemoglobin in response to treatment with erythropoietin (ESF)--the blood plasma factor which, in the normal individual, stimulates red cell production.

In 10 laboratory studies performed on marrow from six individuals, the investigators found that hemoglobin synthesis in cultures treated with ESF was increased many times over that of untreated control cultures. Since hemoglobin synthesis only takes place in dividing and growing cells, this observation constitutes evidence that the stored cells do in fact proliferate.

(more)

The investigators caution that their results apply to only one of the five types of precursor or "stem" cells in the marrow. The proliferative capacity of other elements in frozen stored human marrow remains to be determined.

The investigators reported their work in the October 1972 issue of *Transplantation*. They received support from the National Cancer Institute, the National Heart and Lung Institute, and the National Institute of Allergy and Infectious Diseases.

#

Research Advances

IN THE LITERATURE:
Journal of Nuclear Medicine, April 1972

RADIOACTIVE AMMONIA PRODUCES IMAGES OF MYOCARDIAL DAMAGE--NIH-supported scientists in Chicago have developed a promising new tool for diagnosing myocardial damage. The method employs radioactive ammonia to produce videotape images of damage to the myocardium, the muscular wall of the heart. Existing X-ray techniques do not reveal this damage.

Dr. Paul V. Harper and associates at the Argonne Cancer Research Hospital, a part of the University of Chicago Hospitals and Clinics complex, developed the experimental procedure for imaging the human myocardium. They produced radioactive ammonia and injected the solution into human volunteers, one of whom had symptoms of a heart infarction eight years earlier.

Scientists know that radioactive ammonia concentrates in the liver and bladder and that it will concentrate in the myocardium when injected into the blood vessels. According to Dr. Harper, it follows that radioactive ammonia concentrates in the region of the myocardium where blood vessels exist--not in an infarct where blood circulation has ceased.

Detection and imaging of the radiation from the myocardium were accomplished with a Nuclear Chicago HP Anger Camera. The radiation output was recorded on videotape so that the images of different phases of uptake can be replayed.

For each subject, twenty minutes of continuous recording were required to obtain a single photograph of radioactive emissions from the ammonia concentrated in the myocardium. The ammonia diffused into the myocardium within 30 seconds of reaching the heart.

(more)

The first subject was apparently normal and healthy and the videotape confirmed this. Myocardial scan of the second patient--who was also apparently healthy but admitted a previous episode of severe crushing chest pain--showed a defect in the inferior portion of the left myocardium which represented an old infarct.

According to Dr. Harper, "The use of ammonia as a scanning agent makes possible clinical myocardial images with high count density, good contrast, and low absorbed radiation dose using commercially available imaging equipment." He plans further equipment and technique refinement.

This work is supported by the National Institute of General Medical Sciences. Principle investigator for the project is Dr. Kurt Rossmann of the University. (See *NEWS & FEATURES From NIH*, December 10, 1972, for further information about Dr. Rossmann.)

#

Photo Feature

RARE GOATS TRAVEL TO ENGLAND FOR STUDY OF MUSCLE DEFECT

Four "nervous" goats from the University of Cincinnati Medical Center recently arrived at Cambridge, England, to be used in a collaborative research project on a rare hereditary muscle defect known as myotonia.

Myotonia is a defect in the muscle fiber membrane which permits repetitive production of muscle impulses. This causes the goat to stiffen up and fall over when it is forced to move suddenly from fright or loud noises.

Dr. Shirley Bryant, Professor of Pharmacology at the University of Cincinnati College of Medicine, who is supported by the National Institute of Neurological Diseases and Stroke in his study of myotonic goats, will work with Dr. R. H. Adrian, a specialist in muscle studies at the University of Cambridge. The investigators will use a voltage clamp--not available in the United States for myotonia studies--for making detailed measurements of muscle fiber. These studies will help explain a similar defect occurring in human muscle diseases in conditions known as myotonia congenita (Thomsen's disease) and in certain muscular dystrophies.

Dr. Bryant will remove small samples of intercostal muscle (muscle found between the ribs) from anesthetized goats for study on the voltage clamp. By this method, he hopes to define exactly the defect causing myotonia.

"The increased understanding derived from these experiments may be useful in the design of better therapy or prevention of myotonia," Dr. Bryant says. "It may also extend our basic knowledge regarding the nature of abnormal repetitive firing of excitable membranes--a phenomenon underlying two common human abnormalities, cardiac arrhythmias and epilepsy."

(more)

The myotonia defect, known to be an abnormality of the production of muscle impulse, is said to be the involuntary persistence of voluntary contraction. "The nerve tells the muscle what to do and when to stop, but in myotonia, the muscle continues to contract even after the nerve activity stops," Dr. Bryant explains.

On arrival in England the goats entered quarantine for 56 days to assure that they do not have blue tongue, a sheep disease common in Africa. Dr. Bryant says it is rarely found in the United States.

While the Cincinnati goats are in quarantine, Dr. Bryant continues to study samples of muscle from normal English goats. He dissects a few fibers from the muscle under a microscope, and then places a single fiber into the voltage clamp, where three micro-electrodes penetrate the fiber to measure the electrical mechanism of the membrane of the cell--the mechanism which gives rise to the impulse of the muscle. The voltage clamp holds the cell's voltage constant so that measurements can be made of the currents that occur. This detailed study of the membrane mechanism in myotonia cannot be obtained from any other technique, according to Dr. Bryant.

The investigator will also use the voltage clamp to further test his finding that the unstable cells from myotonic muscle fibers are not permeable to chloride ions. (Chloride permeation is necessary for stable muscle fiber.)

"In the future at the University of Cincinnati we hope to be able to apply this technique to study human muscle," Dr. Bryant says.

(more)

Rare Goats (Cont'd)

Four myotonic goats arrived recently in England, the first since 1938, for use in a study of that rare inherited disease. Myotonia is not painful nor life threatening, according to Dr. Shirley Bryant (right), Professor of Pharmacology at the University of Cincinnati College of Medicine, whose study of myotonic goats is funded by the National Institute of Neurological Diseases and Stroke. (NIH Photo #984)

Farmers sometimes prefer myotonic goats (below) because they usually do not jump over obstacles higher than 20 inches. This useful feature, plus their curious behavior, appear to be the main reasons why the breed has survived. However, the future survival of the myotonic goat for research in muscle disease is uncertain. Researchers maintain colonies of myotonic goats in Cincinnati and Columbus, Ohio; Rochester, Minnesota; Columbia, Missouri; and Nashville, Tennessee. (NIH Photo #985)

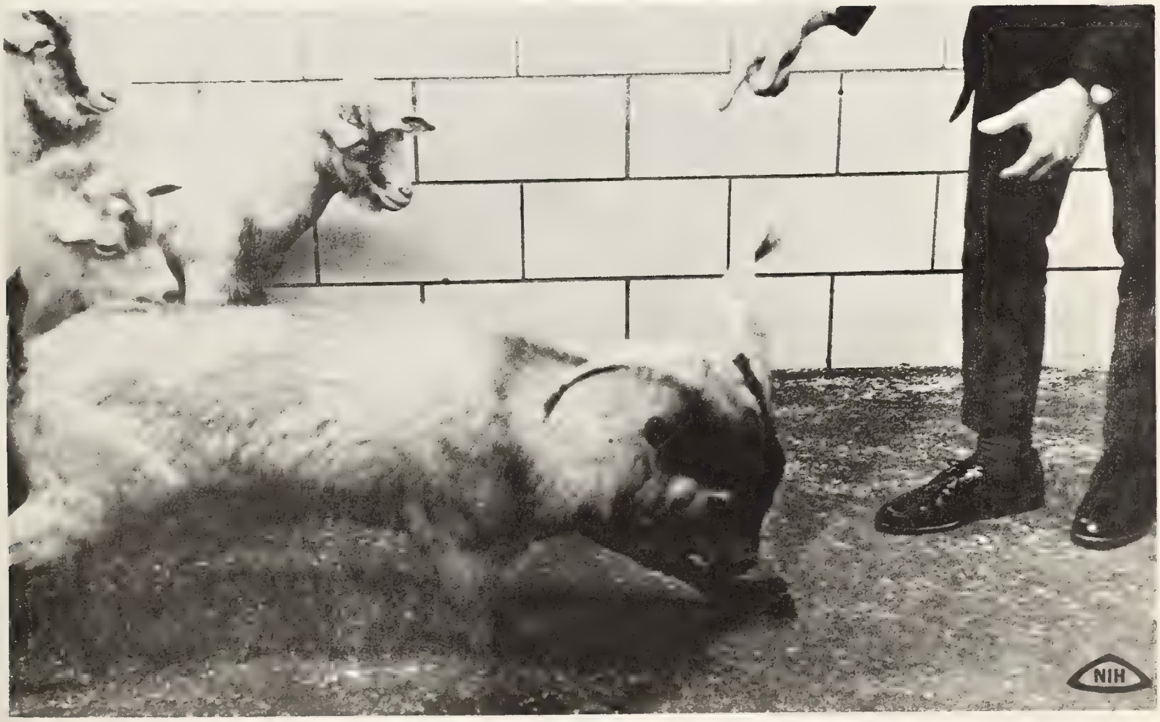


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Photo Feature

PATIENT CAN "PHONE IN" ECG USING PORTABLE TRANSMITTER

A heart patient experiencing transient arrhythmia (irregular heart beats) can now send his electrocardiogram (ECG) across telephone lines without having to leave home. He can use a lower-cost modified version of a portable ECG transmitter designed several years ago by William Holsinger and Kenneth Kempner, engineers in NIH's Division of Computer Research and Technology (DCRT).

The device is especially useful for patients with implanted pacemakers, which contain batteries to supply the voltage for keeping the heart beating rhythmically. If the battery begins to fail, the "paced" heart rate changes. By periodically recording the ECG for analysis, the physician is alerted to worn out batteries and can plan for replacement of the pacemaker.

George Washington University physicians Dr. Herman Klingenmaier, Director of the MEDLAB Computer Project, and Dr. George Rios, Chief of the Pacemaker Clinic, evaluated DCRT's transmitter in the clinic. After finding the transmitter quite useful and economically feasible, they submitted the design to a commercial manufacturing firm. Now, the firm is manufacturing 50 transmitters for patients who will follow this procedure:

The patient phones a technician at the University's Pacemaker Clinic. The technician enters information such as the patient's name into the MEDLAB computer, using a keyboard and television-tube terminal.

The patient then sends his ECG directly into the computer. He places a small sound-producing transducer on the mouthpiece of the receiver, puts his palms on two circular electrodes which pick up his ECG, and sends it to an amplifier and frequency modulating oscillator.

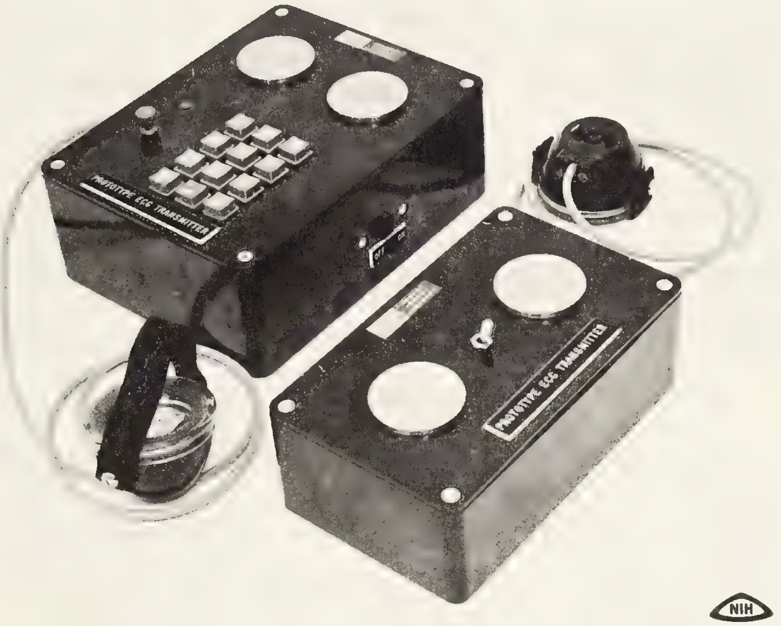
(more)

Portable ECG (Cont'd)

The result is an ECG converted into an FM signal by a process similar to that in an FM radio station. The FM signal is within the frequency range of human speech and passes through the sound producing transducer into the mouthpiece of a standard telephone.

The computer performs a preliminary analysis on the ECG and presents it to the technician, who can immediately inform the patient and the doctor about the condition of the pacemaker.

One version of the ECG transmitter, also designed by DCRT engineers, includes a cluster of 12 pushbuttons. With this model, a patient can communicate directly with a suitably designed computer without the assistance of a technician.



A heart patient can use one of these ECG transmitters to send his electrocardiogram by telephone to a computer without leaving home. He attaches the sound-producing transducer to the telephone mouthpiece and places his hands on the two disc electrodes on the device. The pushbutton model (left) allows the patient to enter his name and other personal information directly into the computer, while the transmitter on the right requires a technician to enter the patient's personal information into the computer. The transmitter was designed by engineers at NIH's Division of Computer Research and Technology. (NIH Photo #986)

#

News Feature

SCIENTISTS FIND FLUORIDE ESSENTIAL TRACE ELEMENT

University of Minnesota scientists, in a study supported by the National Institute of Dental Research, have found evidence that fluoride is an essential dietary element for mice.

Drs. Wallace D. Armstrong, Harold H. Messer, and Leon Singer, of the Biochemistry Department at the University, reached this conclusion when they discovered that a low-fluoride diet leads to a decline in reproductive ability and to severe anemia in pregnant and weaning mice. The anemia findings were reported in the December 13 issue of *Nature*.

When the scientists compared mice given a diet low in fluoride to others given the same diet supplemented with fluoride, they found a marked reduction in the ability to reproduce in animals on the fluoride-deficient diet. In four successive matings the rate of successful pregnancies in animals on the fluoride-supplemented diet never dropped below 96 percent. In contrast by the fourth mating, only 48.1 percent of the low-fluoride mice had successful pregnancies. When these animals were switched to the fluoride-supplemented diet, their reproductive ability soon returned to normal.

This study, published in the September 8, 1972 issue of *Science*, "demonstrates that fluoride satisfies the major criteria for an essential trace element: a deficiency state has been produced in mice on a diet low in fluorides; the deficiency is prevented and cured by addition of fluoride alone to the diet."

It is possible that the decline in reproduction may have been related to anemia, since the same team found that lack of fluoride leads to more severe

(more)

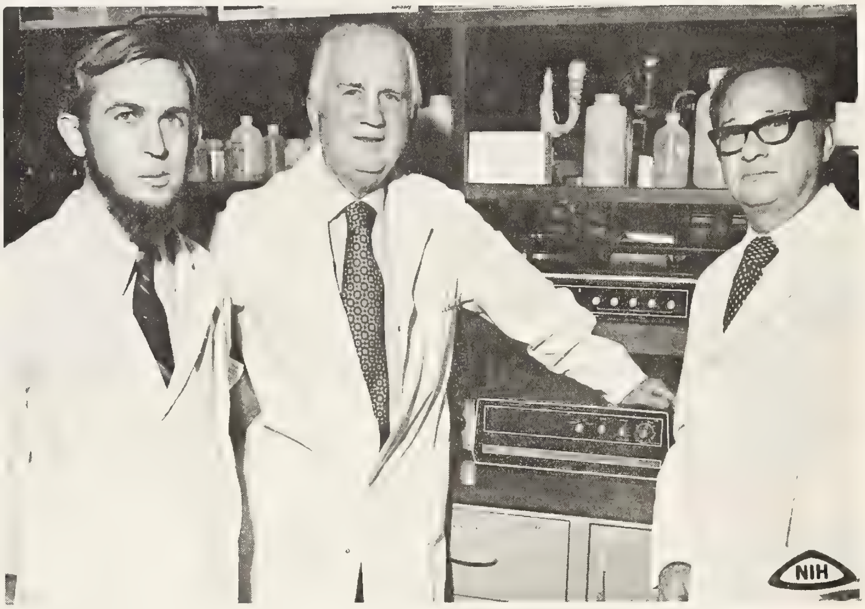
Fluoride (Cont'd)

anemia in mice during pregnancy and weaning than occurs in animals fed a diet rich in fluoride.

The mechanism by which fluoride affects the hematocrit (blood) count is not clear. Whatever the mechanism, it appears that under such stresses as pregnancy and weaning greater amounts of fluoride are needed for well being.

In a related study supported by the National Institute of Arthritis, Metabolism, and Digestive Diseases, Dr. Klaus Schwarz of the Veterans Administration Hospital in Long Beach, California, found that young rats deprived of fluoride did not grow as rapidly as did similar rats given a fluoride supplement. When he added fluoride to the diet of the first group, the growth rate increased 20 to 30 percent.

These studies are important evidence in support of the theory that fluoride is an essential nutrient in the human diet, although there is no direct proof as yet.



Drs. Leon Singer, Wallace D. Armstrong, and Harold H. Messer (from left) have found evidence that fluoride is an essential trace element in the diet of mice. Their research at the University of Minnesota is funded by a grant from the National Institute of Dental Research. (NIH Photo #987)

#

Photo Feature

"X-Ray" by Sonar...

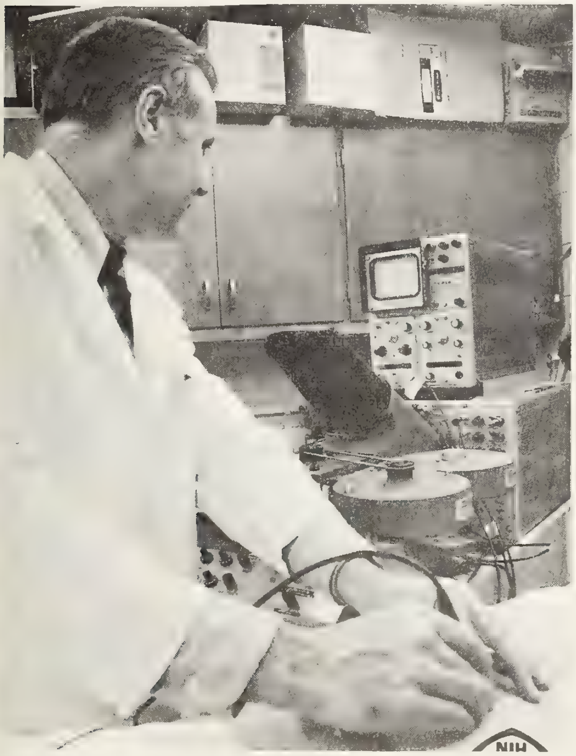
ULTRASOUND MOVIES SHOW HEART CONDITION

Naval sonar may become a medical diagnostic tool for studying the human heart, according to three University of Rochester radiological and biomedical engineering researchers.

Raymond Gramiak, M.D., Robert C. Waag, Ph.D., and William Simon, Ph.D., are using ultrasound to produce motion pictures of the heart's movements which can indicate the condition of the heart without harm or danger to the patient. Their work is supported by the NIH National Heart and Lung Institute.

According to Dr. Gramiak, Professor of Radiology at the University's School of Medicine and Dentistry, "This no-risk setting may allow for the investigation of cardiac processes not now approachable by X-ray techniques."

The investigators use a method that is basically the same as that used by naval vessels to locate underwater objects. They transmit pulses of sound



Dr. Raymond Gramiak of the University of Rochester School of Medicine and Dentistry, watches the patterns made on the face of an oscilloscope by the echoes reflecting from the surfaces of his patient's heart. Computer-assisted interpretation and motion picture display of the results may help physicians diagnose many types of heart disease and injuries which cannot be diagnosed with X-ray techniques. Dr. Gramiak's research is supported by the NIH National Heart and Lung Institute. (NIH Photo #988)

(more)

into the body, and then plot and record electronically the returning echoes from surfaces of the heart and other structures.

The examiner uses a transducer--a device which sends sound pulses and receives the echoes--pressed against the patient's chest. Angling it through an arc, he is able to record the echoes from surfaces through a pie-shaped section of the heart during several heartbeats. The echoes are converted into electrical signals and are displayed on an oscilloscope. The signals are photographed, producing an echocardiographic panorama.

A trained observer can identify the valves, chambers, and walls of the heart in the photo. However, the need for detailed training in the interpretation of these panoramas has hindered the acceptance of this potentially very useful diagnostic tool.

A University of Rochester technician cuts "panoramas" of echoes received from surfaces of the heart's structures and assembles a sequential motion picture of a heartbeat. (NIH Photo #989)

The investigators have developed a method which incorporates the attractive features of diagnostic ultrasound and the desirable aspects of cine radiology (X-ray movies). Early experience with both manual assembly and computer assembly of these images indicates the potential usefulness of this method.

The investigators believe that the technology is available to produce images of high quality in sufficiently short time to make them clinically useful.

#

Medical News Tip

SEARCHING FOR A CAUSE AND CURE FOR MULTIPLE SCLEROSIS--Multiple sclerosis (MS) remains a mystery disease today as it was a century ago: neither the cause nor an effective treatment is known. Primarily affecting young adults in temperate climates, MS is the most common demyelinating (loss of fatty sheath surrounding nerve fiber) disease of man.

The National Institute of Neurological Diseases and Stroke (NINDS) conducts an extensive program of research into the disease. Much of this research is still at the basic test tube level, but work also continues through epidemiological studies.

Currently, NINDS scientists follow three main research approaches in the attack on MS. Because the disease is one of the temperate zone, Institute-supported scientists have conducted numerous epidemiological studies among various population groups with known or suspected high or low rates of the disease.

Another approach is through an understanding of the biochemistry of the disease.

The search for a viral cause for MS represents the third approach. In the past few years, proof that several neurological diseases can be transmitted to animals has given new impetus to this effort.

Some scientists consider the study of MS as an autoimmune disease as still another research approach. However, they believe that the autoimmune process is triggered by a virus in some way.

For additional information on the NINDS multiple sclerosis research program, contact: NINDS Information Office, Bldg. 31, Room 8A-03, NIH, Bethesda, MD 20014, Phone: (301) 496-5751.

#

New Publication:
Hydrocephalus

In hydrocephalus, an abnormal accumulation of cerebrospinal fluid presses on the tissues of the brain causing enlargement of the head, various degrees of brain damage, and convulsions. Sometimes called "water on the brain," the disorder can originate before or at birth or as a result of a variety of ailments that develop later in life.

A new fact sheet from the National Institute of Neurological Diseases and Stroke (NINDS)--*Hydrocephalus*--details the causes, symptoms, prevalence, and treatment of the disorder and outlines NINDS research in this area.

Hydrocephalus often does not become apparent until after the first few weeks of life, the onset being marked by expansion of the skull and prominence of scalp veins. If untreated, the increased pressure on the brain can cause severe headaches, a lag in physical and mental development due to the weight of the head and the impairment of the nervous system, and contractions in the arms and legs as the condition progresses.

According to the fact sheet, proper treatment of the disorder often enables a child to develop normally and achieve full intellectual capacity, depending upon the cause of the hydrocephalus, the stage in life when it developed, and the state of the brain prior to surgery.

NINDS scientists are searching for improved surgical techniques to prevent mental retardation in hydrocephalic patients as well as working to improve diagnostic techniques. Also, better use of medication may one day enable doctors to control hydrocephalus without surgery.

Science writers can obtain a copy of *Hydrocephalus* from: NINDS Information Office, Bldg. 31, Room 8A-03, NIH, Bethesda, MD 20014.
Phone: (301) 496-5751.

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News Releases Issued

(Summaries of NIH releases sent out since the last issue. For a copy of any of these, please write or call.)

CARCINOGENIC FIBERS--Microscopic fibers of a certain size can cause cancer in laboratory rats, regardless of the chemical composition of the fibers, according to Dr. Mearl F. Stanton of the National Cancer Institute (NCI). The scientist believes that the cancer-causing activity of asbestos, for example, is due to its fibrous structure. Dr. Stanton experimented with laboratory rats to test the ability of various fibrous and non-fibrous substances to cause cancer of the membrane surrounding the lungs. Results showed that very fine fibers of asbestos, glass, or sapphire caused a high incidence of pleural cancers in the animals, while coarse fibers or powdered material of the same compositions only rarely caused cancer. The cancer-causing fibers were between one-half and five microns in diameter and less than 80 microns long, that is, less than one-hundredth as thick as an eyelash and under one-tenth as long.

CANCER DRUGS--NCI has announced the first formal agreement between the Institute and Bristol Laboratories, a division of Bristol Myers Company, for the economical, rapid distribution and testing of certain cancer drugs. Of the drugs covered by the agreement--BCNU, CCNU and methyl-CCNU--only BCNU testing in animals and its clinical evaluations in cancer patients have been completed at this time. Under the agreement, if the Food and Drug Administration (FDA) approves BCNU, Bristol Laboratories will manufacture and market the drug at a reasonable cost to the consumer. The firm is obligated to market only BCNU. NCI will continue to foster research and to collect and evaluate cancer therapy data for the other drugs. If the FDA approves the drugs for use in human cancer, Bristol Laboratories will be offered the first opportunity to market them.

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January 25, 1973

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NEWS & FEATURES From NIH January 25, 1973

Research Advances

PROLONGED SURVIVAL FOUND FOR SECOND HUMAN KIDNEY TRANSPLANTS

A major concern of kidney transplant patients is "What will happen if my first kidney transplant fails after only a few months? What are the chances that a second kidney transplant will survive and for how long?" It might be expected, based on classical concepts of transplantation immunity, that a person who rejects his first kidney transplant rapidly would reject his second transplant even more rapidly.

However, this is not always the case. A recent study supported in part by the National Institute of Allergy and Infectious Diseases (NIAID) revealed that the survival rates for first and second kidney transplants from cadaver donors were almost exactly the same.

This study of 257 second grafts and 1497 first grafts was carried out by Dr. Gerhard Opelz and Dr. Paul I. Terasaki of the University of California School of Medicine at Los Angeles. Their initial findings, which confirmed those of several other investigators, were, on the surface, very surprising. One might expect that if the first transplant immunizes the patient or is rejected by immunologically responsive patients, second grafts into the same patients would be rejected at a higher rate.

To investigate this paradoxical situation further, Drs. Opelz, Terasaki, and Max R. Mickey analyzed the survival rates of 264 second grafts from cadaver donors transplanted between January 1967 and December 1971. All patients had lost their first transplants from either related or cadaver donors.

(more)

The scientists found that the overall first transplant survival rate was almost identical to the overall survival rate for the second in this group of patients. After one year, the survival rate (51%) for the second kidney transplants survived was exactly equal to that of the first attempts.

Thus, at first glance, it seemed to the investigators that the first kidney transplant did not in any way condition the patient, since the survival rates of the first and second groups were identical. Upon closer examination, however, the scientists found distinct differences in second graft survival rates when they classified patients according to the length of time it took them to reject their first transplanted kidneys.

The most interesting group of patients were those who rejected their first graft relatively slowly, that is, after three months. These patients had a one-year second graft survival rate of 60%, significantly higher than the overall first graft survival rate. Moreover, recipients of initial kidney transplants from cadaver donors with a survival rate of 40% at one year had a considerably improved second attempt survival of 60% at one year when retransplanted with kidneys from cadaver donors. A prolongation effect appears to have been induced by the rejection of the first transplanted kidney.

One explanation put forth by the scientists for the prolonged survival rate after repeat transplantation for patients who were "slow rejectors" is that the first graft may, under certain conditions, induce "enhancement of retention or tolerance" to the second graft. These patients may form protective or "enhancing antibodies" as a result of the immunizing effects

(more)

of the first graft. If the presence of enhancing antibodies can be firmly established, these antibodies may prove useful in prolonging the life of kidney transplants. This is an area that is being investigated by many scientists.

Another (but less likely) explanation requiring further evaluation is that some of the patients are inherently "slow rejectors" with poor immunologic responsiveness and that the procedure only serves to differentiate people with different degrees of ability to react to the immunologic stimulus provided.

Drs. Opelz and Terasaki reported their findings in the November 10, 1972 issue of *Science*. They also received support from the National Institute of Arthritis, Metabolism, and Digestive Diseases. The NIH Division of Research Resources provided grant support for the UCLA Health Sciences Computer Facility used in this study.

#

Research Advances

STUDY OF HGH IN MUSCULAR DYSTROPHIES MAY LEAD TO NEW TREATMENT METHODS

The use of human growth hormone (HGH) in muscular dystrophy patients has opened up new areas of research into the causes and possible treatment of the disease.

NIH-supported investigators at the Emory University School of Medicine report that patients with two of the major types of muscular dystrophies responded favorably to human growth hormone in short-term studies. The patients gained weight in muscle tissues although the hormone did not produce any consistent change in muscle strength.

As a result of their studies, the investigators--Samuel B. Chyatte, M.D., Daniel Rudman, M.D., and colleagues--began a program of long-term HGH treatment at the University's Clinical Research Facility. The dystrophy patients are carefully monitored to see if they continue to gain weight or if they become stronger. The studies are supported by grants from the NIH Division of Research Resources.

According to the investigators, patients with myotonic dystrophy and limb-girdle dystrophy showed an early good response to HGH. Patients with the Duchenne type of muscular dystrophy, the most common form (approximately 90 percent of all muscular dystrophy patients have the Duchenne type), showed an opposite effect when the researchers administered human growth hormone. Leakage of enzymes from muscle cells (an indication of muscle damage) was observed following treatment with HGH in patients with this type of dystrophy.

(more)

This finding led Drs. Chyatte and Rudman to use diethylstilbestrol (DES), a synthetic female hormone, in Duchenne patients to help slow down the growth process. As a result, DES had a muscle-building effect on the Duchenne patients similar to the effect of HGH in the other dystrophy types. The Emory physicians point out that the Duchenne type of muscular dystrophy affects males only and therefore only male patients in the study will receive the drug.

Dr. Chyatte believes that "the apparent catabolic response (tissue-destructive) of the children with Duchenne muscular dystrophy to HGH is perhaps the most striking finding" in his studies. A catabolic response to growth hormone has not been described before in humans or in other animals.

According to the physician, "HGH was, therefore, not only rejected as a potential therapeutic agent in the Duchenne form of dystrophy but also may be implicated in the pathophysiology of the disorder."

Dr. Rudman adds that, "In some ways, Duchenne seems a mirror image of the other types of dystrophies we've studied. It could be a basic biochemical defect which is causing this unusual reaction to growth hormone."

Both investigators believe that their observations have opened up a new approach to the muscular dystrophy problem. Further investigation may better define the pathophysiology of these disorders and may also provide new diagnostic tests.

Widespread use of HGH as a therapeutic agent in medicine will depend largely on whether HGH or an analogue of HGH can be synthesized. Emory scientists in the school's Department of Biochemistry have succeeded in isolating the active portion of the HGH protein molecule and are now attempting

(more)

to determine its chemical structure. Once accomplished, the active center can be synthesized and the supply of HGH will be greatly increased.

Dr. Chyatte and Dr. Rudman reported on their HGH trials at the Southern Medical Association meeting in New Orleans, November 1972.

#

Research Advances

ESCHERICHIA COLI IDENTIFIED AS CAUSE OF INFANTILE DIARRHEA

Each year in the United States, thousands of babies are hospitalized as a result of acute infantile diarrhea. Although many microorganisms are associated with the disease, the causative agent of infantile diarrhea has rarely been identified with certainty.

It now turns out, as a result of research supported in part by the National Institute of Allergy and Infectious Diseases, that certain strains of the common intestinal bacteria Escherichia coli (E. coli) may be responsible for most acute infantile diarrhea. The strains, the so-called "enteropathogenic" (EPEC) variety, grow in the upper gut and secrete a toxic material (enterotoxin) that causes a net secretion of salt and water into the intestine from the blood plasma, thus causing diarrhea.

EPEC strains have long been suspected as the cause of acute diarrheal epidemics in nurseries of newborn infants. However, simple culture techniques have usually failed to isolate the bacteria.

Using a special assay technique in infant rabbits, Sherwood L. Gorbach, M.D., and Chandra Mohini Khurana, M.D., positively identified enteropathogenic E. coli strains in stools from 24 of 29 children hospitalized for dehydration and toxicity due to diarrhea at Cook County Hospital, Chicago. The investigators found that two or three enterotoxin-producing strains were often present in the same stool specimen.

In contrast, they were able to identify the enteropathogenic strains in only nine of the children when using simple culture techniques. Twelve

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types of E. coli were isolated from stools of nine well infants in a control group, but none of the strains were enteropathogenic based on the infant rabbit assay.

Based on current knowledge, it appears that the events in toxigenic E. coli diarrhea resemble those in Asiatic cholera caused by the organism Vibrio cholerae. Although E. coli enterotoxin differs biochemically and immunologically from cholera enterotoxin, it is possible that the physiologic mechanisms in the intestinal epithelium may be similar.

For example, cholera toxin appears to cause adenyl cyclase to be produced, which in turn causes an increase in the levels of cyclic AMP, known to be the mediator of the action of many hormones in various tissues. It is thus possible that the increase in cyclic AMP could stimulate secretion in intestinal cells. The toxin from EPEC strains could act in the same way in the production of infant diarrhea.

Increased understanding of the mechanism by which cholera enterotoxin and E. coli enterotoxin cause diarrhea could lead to an improved treatment for the respective illnesses. Such a treatment should *halt* the physiological defect in the cells rather than *correct* its secondary effects, namely diarrhea and dehydration.

Currently, infantile diarrhea, caused by what is thought to be normal E. coli strains, is generally treated with the antibiotic neomycin. If most infantile diarrhea is caused by toxigenic E. coli strains, however, treatment of infants might be altered to include fluid and salt replacement therapy as is done for cholera victims.

(more)

To date, large scale investigations of toxigenic E. coli in diarrhea have been limited by the need to use animal models in the assays. A biochemical assay for enterotoxin would eliminate this animal model requirement and would make possible the assessment of the importance of these strains in diarrheal diseases. Work on developing such a biochemical assay is underway.

The investigators reported these findings in the October 19, 1972 issue of the *New England Journal of Medicine.*

#

Photo Feature

Second Leading Cause of Blindness...

OPHTHALMOLOGIST STUDIES ONCHOCERCIASIS IN AFRICA

In certain regions of Africa, blindness is an accepted way of life.

"It's as natural to these people as childbirth; going blind is to be expected," explains Dr. James P. Ganley, an ophthalmologist and epidemiologist in the National Eye Institute. Dr. Ganley recently served on one of seven World Health Organization (WHO) teams which have been organized to investigate the prevalence of a systemic disease which is the second leading cause of blindness in Africa.

The disease--onchocerciasis--is transmitted by bites from infected flies. Victims of onchocerciasis host a strain of filarial worms that cause the development of skin nodules and eventual blindness. Onchoceral

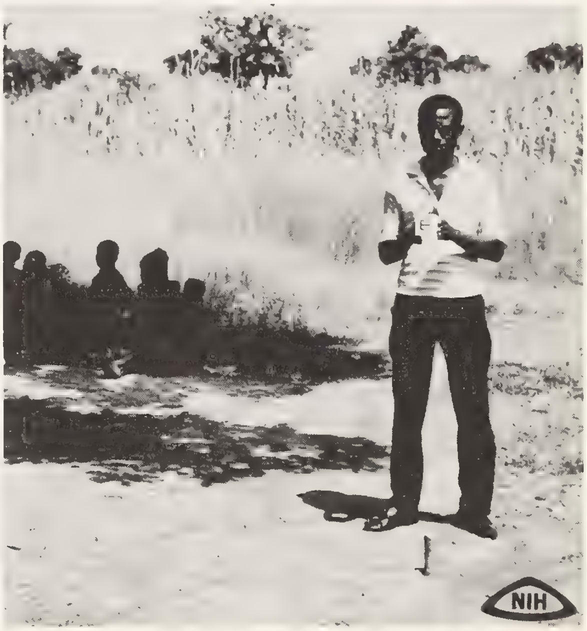
(more)

Dr. Ganley snips a small slice of conjunctiva (mucous membrane which covers the front part of the eye) from a study participant. This biopsy specimen is used to determine the microfilial count in the eye. (NIH Photo #990)

infection occurs early in life, but visual impairment usually progresses slowly. By the age of 50, however, over half of the population examined by the WHO team were blind from this disease.

WHO's Seven Nation Volta River Onchocerciasis Treatment Project is a large-scale, long-term program directed toward the control of the disease in the region of West Africa drained by the Volta River and its tributaries. Because the fly larva which transmits onchocerciasis requires oxygenated water for its life cycle, blindness rates are highest near the rivers.

"As people become blind in the villages closest to the rivers and streams, they also die more quickly; eventually whole villages die out, and large tracts of very fertile land are left uninhabited," Dr. Ganley said. He went on to explain that the people are so attached to the land that they will not move away even when they know about the disease and the eventual blindness.



Participants in the study were examined for signs of onchoceral infection, including loss of vision. To determine visual acuity of the participants, the WHO team administered the "illiterate E" test which consists of identifying a series of "E's" in decreasing size that are rotated to point in different directions. (NIH Photo #991)

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Dr. Ganley, along with other members of the WHO team, spent one month gathering base-line data on the prevalence of onchocerciasis in the Upper Region of Ghana and the frequency of blindness associated with the disease.

Six villages, ranging in population size from 55 to 464 people, were selected to participate in the study. Blindness rates varied among the villages, but overall, approximately nine percent of the total population was socially blind (that is, visual acuity of 20/200 or worse in the better eye). Total blindness (no light perception in either eye) for the entire population was 2.7 percent.

These blindness rates compare rather dramatically with those of this country. For example, the WHO team found a rate of social blindness in the Upper Region of Ghana that is approximately 35 times higher than that for the non-white population of the United States in 1968. Dr. Ganley estimates that about 70 percent of blindness in the area he studied is caused by onchocerciasis.

According to Dr. Ganley, this type of preliminary study is a necessary part of a control program. Without such data, it would be impossible to determine the scope and seriousness of the disease. Furthermore, once a control program is started, base-line data is the only way to evaluate periodically the success of the project.

Presently, there are two drugs available for treating onchocerciasis, but since both have serious side effects the only way to eliminate onchocerciasis is to eradicate the fly whose bite transmits the disease. This can be done through a massive and prolonged spraying project. The

(more)

larvae of the fly are extremely sensitive to a slightly higher concentration of DDT than is contained in rain water in the United States. Continuous spraying would cover all known waterways in an area wide enough so that there would be no threat of spill-over of flies from surrounding unsprayed regions. Dr. Ganley estimates that such a spraying project would continue for 10 to 15 years and at a large cost.

He emphasized, however, that "given sufficient planning, time, and effort, I think it will be feasible to eliminate onchocerciasis from Africa."

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Photo Feature

ALASKAN WILD RODENT POSSIBLE RESEARCH MODEL

Arctic biologist Robert A. Dieterich, DVM is researching the special natural characteristics of the collared lemming (Dicrostonyx groenlandicus) in Fairbanks, Alaska. This species of wild rodent, found only in the Arctic regions, may be the most useful animal model yet discovered for studies of cholesterol level and mammary tumor as well as for research on progressive degeneration of the kidneys due to infection.

The Arctic wildlife research project being conducted by the Institute of Arctic Biology at the University of Alaska is supported by the NIH Division of Research Resources. (NIH Photo #992)

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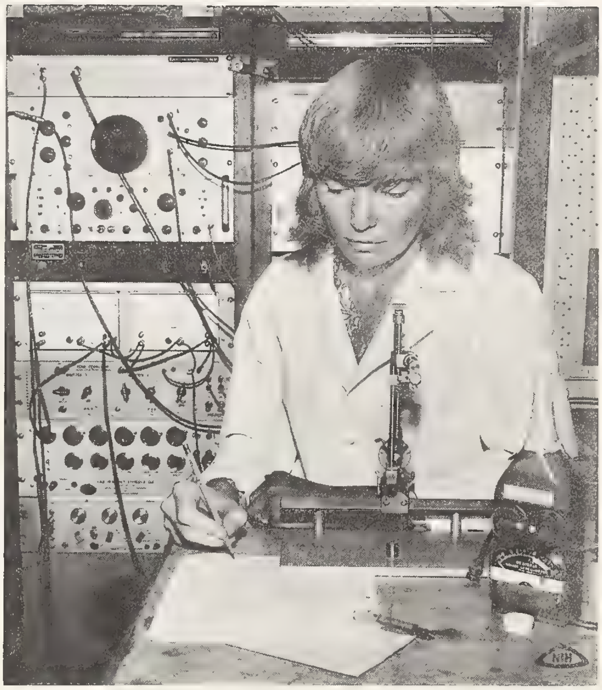
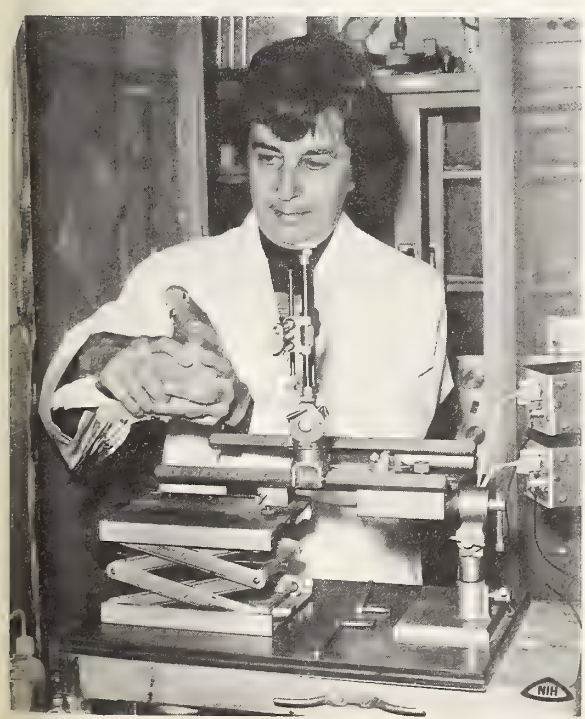
Photo Feature

Grantees at UCLA...

SCIENTISTS SPECIALIZE IN NEUROLOGICAL RESEARCH





At the University of California, Los Angeles, School of Medicine (UCLA), National Institute of Neurological Diseases and Stroke grantees perform vital research in the neurosciences. Clockwise from top left, Mary A.B. Brazier, D.Sc., computes brain potentials for her epilepsy research. Professor of Anatomy and Physiology, Dr. Brazier has been associated with UCLA for 12 years. Jennifer S. Buchwald, Ph.D., Associate Professor of Physiology, examines neuronal changes in the early phases of learning. She has been associated with the school for 10 years. Bernice Wenzel, Ph.D., Professor of Physiology, measures the olfactory function in the pigeon to elucidate the mechanism by which birds smell. She has been at UCLA for 12 years. (NIH Photos #993, #994, #995)

#

Medical News Tip

ATTACKING THE PROBLEM OF HYPERTENSION--The recent National Conference on High Blood Pressure Education tells only part of the story of the National Hypertension Program. The Program seeks ways to reduce the morbidity and mortality of hypertension. Hypertension is a major health problem because about ten percent of all Americans are hypertensive.

As part of the Program, the National Heart and Lung Institute (NHLI) is operating the Hypertension Detection and Followup Program involving 14 clinical centers and a coordinating center.

The centers are working to determine the efficacy of anti-hypertensive therapy for about 10,500 people who are found to have hypertension. Results will not be fully known for several years, partly because a person's blood pressure may be abnormally high for many years before serious damage is apparent.

The coordinating center at the University of Texas supervises training of home interviewers and blood pressure technicians. The clinical centers are at Mount Sinai Hospital, Minneapolis; Albert Einstein College of Medicine, Bronx, NY; University of California, Davis; Michigan State University, East Lansing; Emory University, Atlanta; University of Utah, Salt Lake City; Georgetown University, Washington, DC; Boston City Hospital; Cedars-Sinai Medical Center, Los Angeles; Northwestern University, Chicago; University of Maryland, Baltimore; Evans County (Georgia) Health Department; University of Mississippi, Jackson; and University of Alabama, Birmingham.

For additional information on the NHLI Hypertension Detection and Followup Program, contact: NHLI Information Office, Building 31, Room 4A-10, NIH, Bethesda, MD 20014, phone: (301) 496-4236.

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New Publication:
Fact Sheet: Subacute Sclerosing Panencephalitis

Subacute sclerosing panencephalitis (SSPE), or Dawson's encephalitis, is a chronic progressive neurological disease of the central nervous system. affecting persons from five to 20 years of age. A fatal disease, death from SSPE usually occurs six months to five years after onset.

A new fact sheet on SSPE from the National Institute of Neurological Diseases and Stroke (NINDS) describes the signs of the disease, its frequency and causes, and details NIH research in this area.

According to the publication, SSPE appears to be caused by the "red" measles virus (rubeola). The virus is present in the body for many years after acute measles infections. Apparently, measles acts as a slow, suppressed infection with the brain cells and lymph nodes. This abnormal response to an acute measles infection happens more frequently when the infection occurs during the first two years of life.

SSPE occurs at a rate of about one per 500,000 children in this country, appearing most often in the Southeastern states. The disease occurs three times as frequently among boys as girls.

NINDS Supports studies on SSPE at several medical centers as well as at NIH. A major step in the conquest of the disease was the discovery of the measles virus as the apparent cause.

For a copy of the fact sheet on SSPE, contact:

Information Office
NINDS
Bldg. 31, Room 8A-03
NIH, Bethesda, MD 20014
Phone: (301) 496-5751

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News Releases Issued

CORONARY ARTERY BYPASS--The Clinical Cardiac Disease Branch of the National Heart and Lung Institute is currently inviting contract proposals for a series of carefully controlled studies to evaluate the effectiveness of coronary artery bypass surgery for improving the blood supply to ischemic areas of heart muscle and for relieving angina pectoris and other clinical manifestations of coronary artery disease. Proposals are also being invited for a Coordinating Center to collect and process data emanating from the clinical trials. The proposed studies are a result of the recent upsurge in enthusiasm for this surgical procedure and the limited information on its long-term effectiveness. The studies will be carried out in two phases. Phase I will involve the development of detailed protocols for collaborative studies comparing coronary artery bypass with medical management in sharply defined groups of patients. In Phase II, definitive studies will be undertaken after approval of the collaborative protocols.

EYE DISEASES--An investigation into the prevalence of four of the most common causes of blindness and visual disability recently began in Framingham, Massachusetts. Sponsored by the National Eye Institute, the study is the first large-scale attempt to determine the prevalence of eye diseases, as opposed to blindness, in a well-defined and closely followed population. The study will also seek to identify factors which increase the risk of developing any of the four diseases under investigation--senile cataract, senile macular degeneration, chronic simple glaucoma, and diabetic retinopathy. Finding such factors could lead to means of preventing

(more)

these eye diseases. Even negative findings will be useful in narrowing the search for the causes of these disorders. The four-year study will be conducted by the Boston University School of Medicine's Department of Ophthalmology and will involve examination of approximately 3500 people.

NEW RESEARCH FACILITY--The National Cancer Institute (NCI) has announced the award of a contract providing initial two-year support totaling $2.1 million to the American Health Foundation to assist in the construction of a new Health Research Institute. The new Institute, to be located in Westchester County, New York, will focus on cancer prevention research for the NCI National Cancer Program. Research at the new facility will be devoted to environmental causes of cancer, which are believed responsible for nearly 90 percent of all cancers. Studies are planned on the influence of diet, hormones, air pollution, and other environmental factors on the onset and development of cancer. Ground-breaking for the new research facility will begin early in 1973, with completion of the construction forecast for autumn 1974.

NIH ASSOCIATESHIPS--Applications are now being accepted for Clinical, Research, and Staff Associateships at NIH. The Associateships and two-year positions offering unusual opportunities for training and experience in clinical and laboratory investigation for young physicians and dentists from most of the health specialties and basic science disciplines. The deadline for receipt of applications is March 2, 1973. Interviews will be conducted

(more)

May 7 through 25 and successful candidates will be notified of their acceptance on June 11. A 1973 catalog, which describes the program, and application forms are available from: Chief, Clinical and Professional Services, NIH, Clinical Center, Room 1S229, Bethesda, Md. 20014.

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SPECIAL HEALTH CAREER OPPORTUNITY GRANTS

NEWS&FEATURES FROM NII
NIH Portfolio on Special Health Career Opportunity Grants...January
NIH BUILDING 31, Room 2B-10 * Bethesda MD 20014 * [301] 496-12
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U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE ■ Public Health Service ■ National Institutes of Health ■ Office of Information ■ Bethesda, Maryl

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INTRODUCTION: SPECIAL HEALTH CAREER OPPORTUNITY GRANTS

By George Blue Spruce, Jr., D.D.S., M.P.H.
Director, Office of Health Manpower
Opportunity, Bureau of Health Manpower
Education

Black Americans, Spanish-surnamed Americans and American Indians--minorities with some of the worst health problems in the United States--are grossly underrepresented in the health professions.

Almost one of every six Americans is a member of one of these minorities. In 1970 they comprised more than 16 percent of the total population of 203 million. These minorities are growing faster than the general population.

Clustered in big city ghettos and barrios and hinterland villages and reservations, minorities have extraordinary health problems. In comparison to whites:

* Nonwhite Americans die seven years sooner;
* Nonwhite babies die in infancy almost twice as often;
* Nonwhite mothers die in childbirth four times as often.

The scarcity of minority health professionals is linked with the uneven distribution of health personnel throughout the country. More than 134 counties and thousands of communities lack a physician. Millions of Americans do not have ready access to a physician.

Hardest hit by the uneven distribution of health personnel are the impoverished and poorly educated who live in less attractive inner-city and rural areas.

The uneven concentration of health manpower and the underrepresentation of minorities in the health professions were major concerns of Congress in considering renewal of support for the training of health professionals.

To help alleviate these and other problems, a section on Health Manpower Education Initiative Awards was included in the Comprehensive Health Manpower Training Act of 1971 (P.L. 92-157).

Under the Health Manpower Education Initiative Awards program, Special Health Career Opportunity grants are authorized to recruit into the health professions and other health fields disadvantaged students, especially from minorities, and students likely to practice in underserved areas. The health professions included are medicine, osteopathy, dentistry, optometry, pharmacy, podiatry, and veterinary medicine.

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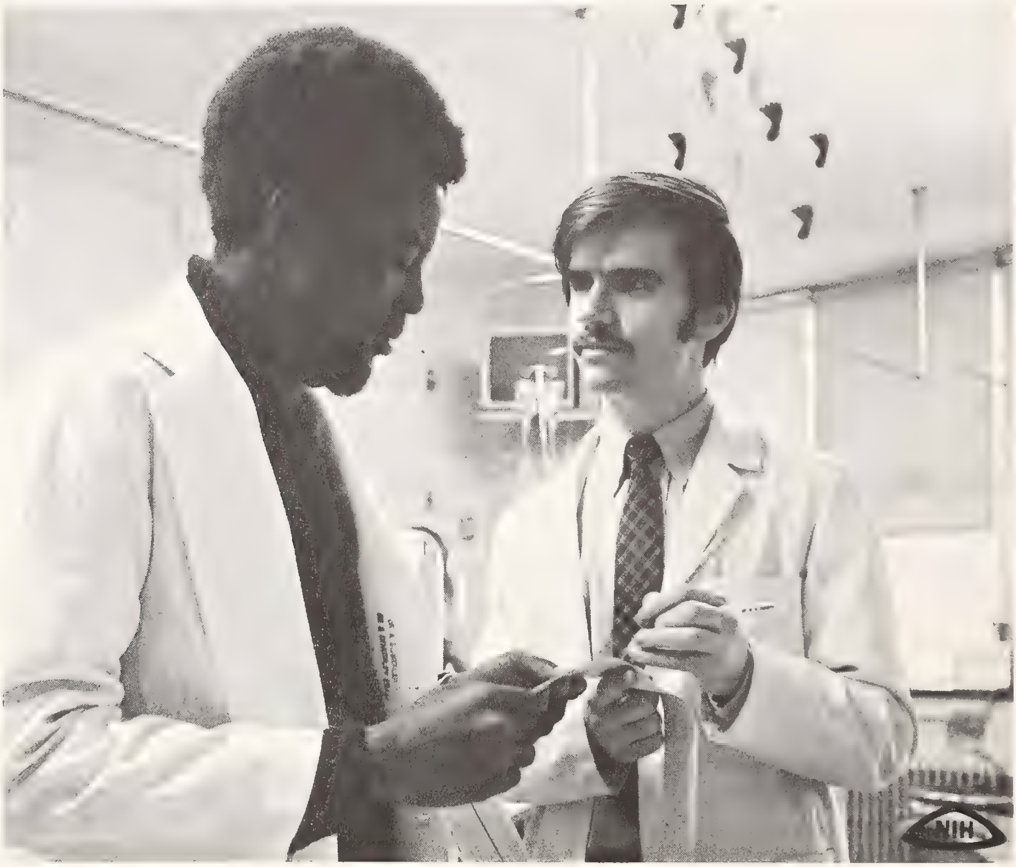
INTRODUCTION

These grants are administered by the Office of Health Manpower Opportunity within the Bureau of Health Manpower Education, a component of the Department of Health, Education, and Welfare's National Institutes of Health. This office deals with the concerns of Black Americans, Spanish-surnamed Americans, American Indians, and women. The office also addresses the health manpower problems of other disadvantaged groups such as poor whites, Asian Americans, Hawaiians, and Filipino-Americans.

Special Health Career Opportunity Grants are awarded for projects to identify and enroll in health professions schools or other health training individuals whose background and interests make it likely that they will practice in rural or other shortage areas.

Grants are also awarded to: (1) identify disadvantaged students with potential for health training, (2) enroll them in health schools and (3) assist them in completing training. For students not qualified to enroll, postsecondary or other training to prepare them for admission is authorized.

The long-term goal is to achieve a representation of minorities in the health professions at least equal to the representation in the general population.



TAHLEQUAH

Cherokee County, Oklahoma,has only five registered physicians and surgeons serving a population of over 20,000, including 3,000 Cherokee Indians. Neighboring Adair County, rated as one of the most impoverished in the Nation, has even fewer physicians and surgeons for its Cherokee population of almost 5,000.

This shortage of medical care in a mountainous country with poor communications and inadequate transportation documents the need and provides the motivation for the Eastern Oklahoma Indian Health Careers Project.

Extensive community development programs have been operating in eastern Oklahoma for a number of years through the cooperation of the University of Oklahoma in Norman, the Cherokee Nation, and the Bureau of Indian Affairs. The community development staff reported an urgent need for additional medical assistance outside the Indian Health Service hospital and clinics for the backwoods regions.

The recruitment and training program that evolved from the recognition of this need will benefit not only the population of eastern Oklahoma --encompassing fourteen Indian tribes with a total of 67,000 members --but also the over 2,000 Indians in area colleges and thousands of promising high school students. Program Director Boyce Timmons of the University of Oklahoma explains:

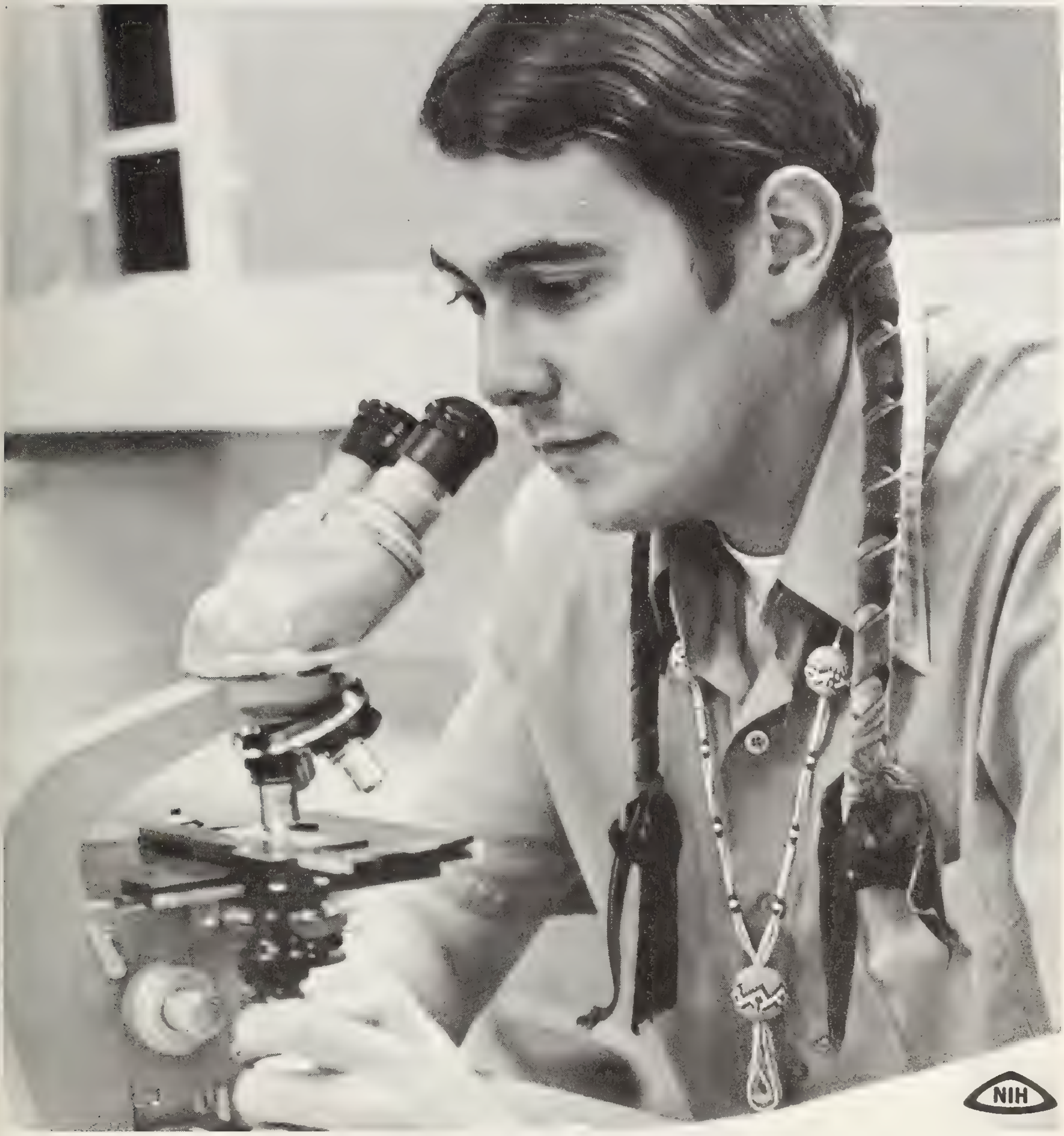
"Hopefully, we can find potential candidates for admission to medical school and give them tutorial assistance, summer institutes, and special training to build them to an academic level at which they can successfully compete with other students in a medical sciences program."

Area educational coordinators, community health representatives, tribal representatives and welfare workers will initially be involved in identifying high school and college students with an interest in and potential for medical professions. Motivating factors such as special counseling, films, and tutoring will be followed up by weekend support classes and a summer program designed to expand educational opportunities in science-related fields in rural areas.

Although seven colleges in Oklahoma will be available as academic training sites, the primary educational facilities will be Northeastern State College and Hastings Indian Hospital, both in Tahlequah. The special weekend and summer classes will be supplemented by trips to hospitals and lectures from area medical staff.

Taken together, the elements of the project will hopefully give deserving students an opportunity to follow a career in one of the health fields while providing eastern Oklahoma with a much-needed supply of well-trained medical personnel.

TAHLEQUAH, OK--Health Occupations Instructor Phyllis Proctor takes the blood pressure of a nurses' aide trainee (upper photo) while two other students obser the procedure. The Cherokee Hills Skills Center offers training programs for nurses aides, ward clerks, dental assistants, and medical records clerks. In lower photo, Dr. Hilary Connors teaches a Maternal Child Health Workshop. Onc trained, these women will be able to provide prenatal and postnatal home care to area residents. The National Institutes of Health, through the Bureau of Health Manpower Education, is administering the Special Health Career Opportu grants. NIH is an agency of the U. S. Department of Health, Education, and Welfare. (NIH Photo #0-1)



ALBUQUERQUE, NM--Jim West, a Cheyenne Indian from Oklahoma, adjusts his microscope in a laboratory at the University of New Mexico, where he is a first-year medical student. West, a former Baptist minister, takes part in a Basic Science Enrichment program which prepares minority students for medical school by training them in basic science. The program will be expanded under a Special Health Career Opportunity grant from the Bureau of Health Manpower Education of the National Institutes of Health. NIH is an agency of the U. S. Department of Health, Education, and Welfare. (NIH Photo #0-2)

TUCSON, AZ--Young students benefit from the "ladder concept" that underlies the Med-Start program operating out of the University of Arizona's College of Medicine. Individuals at the professional or preprofessional level help college students who in turn encourage high school students and junior high students. The project is designed to create a positive change in the communit attitudes toward education, particularly in the field of health sciences. Awar of grants for Special Health Career Opportunity programs are made by the Burea of Health Manpower Education of the National Institutes of Health, an agency o the U. S. Department of Health, Education, and Welfare. (NIH Photo #0-3)

AUGUSTA, GA--James Lane, a sophomore at Columbia University in New York, works at his lab station on his research elective--"Isolation and Characterization of Autolysins from Bacillus Psychrophilus." His findings were presented at the culminating activities of the 1972 Health Science Project for Minority Group Students at the Medical College of Georgia. The Bureau of Health Manpower Education has awarded grants for Special Health Career Opportunity. BHME is a component of the National Institutes of Health, an agency of the U. S. Department of Health, Education, and Welfare. (NIH Photo #O-4)

OAKL

OAKLAND, CA--Dr. David Teegarden (right), staff physician at La Clinica de l Raza, discusses a blood sample with Antonio Spampinato, a senior in biology Hayward State, and another student volunteer. Funds of the Bureau of Health Manpower Education are awarded for the operation of Special Health Career Opportunity grants. BHME is a component of the National Institutes of Healt which is an agency of the U. S. Department of Health, Education, and Welfar (NIH Photo #O-5)

OAKLAND

Between December of 1970 and May of 1971, the 40,000 residents of the Fruitvale district of Oakland lost 17 of the 35 physicians in the community. That May, with less than $300, David Hayes-Bautista opened a small free clinic geared toward Chicano health care delivery. Within two days, La Clinica de la Raza was booked over a month in advance.

Lack of funds with which to pay health professionals and a shortage of doctors with time to spend with the clinic shifted the major portion of the workload to student volunteers. As the clinic expanded, however, the student role in its operation evolved into a valuable program which recruits and trains undergraduate students to work in the clinic. In return, the clinic provides tutoring, counseling, and motivation for its student workers, hoping that many of them will pursue health professional careers and remain in the Chicano health care delivery system once their education is completed.

Recruiting takes place at about 20 Bay Area colleges and universities through various Chicano organizations and minority studies departments. Students who indicate an interest in the clinic program review their academic records with a counselor, who refers them to the nearest of the five Bay Area clinics.

At the clinic, the second or third year undergraduate student comes in contact with a graduate professional student. Esther Picazo, program director for the Bay Area Raza Coalition for Health, describes the role of the health professionals:

"By having them structure programs with the directors of the clinics, we are involving them in coordinating a training program that uses their skills as dentists, doctors, and pharmacists as well as giving them an administrative skill--setting up a program, using funds, providing stipends, and being responsible for an area of health care delivery that isn't limited to your discipline."

She goes on to explain the underlying purpose of the program: "We needed to work with students in college and provide some form of remuneration and training in our clinics. By motivating them positively, reinforcing their commitment, and augmenting their skills in a health care facility like one of the five Bay Area free clinics that are staffed by community workers and health professionals, we would hope to feed them into the health care delivery system, but one that is more or less tailored to our needs."

Since its opening, the clinic has grown from a tiny general medical facility to encompass the field of pediatrics, well-baby care, pharmacy, ophthalmology, podiatry, dermatology, family planning, and dentistry. The core staff of 16, most of them working part-time or in a consulting capacity, handles a patient load of 150 to 200 patients each week with the help of about 35 students and community volunteers ranging in age from 12 to 55.

Student involvement in all aspects of the clinic's operation--from translating to lab work--has motivated many to change their course of study to a health-related field and has provided a mechanism for feeding more Chicano health professionals into a system that desperately needs them.

ITTA BENA, MS--Cleotha Wilson, instructor in the Health Occupation Potential (HOP) program at Mississippi Valley State College, tutors a group of students in mathematics (at left). Below, Dr. Silas Peyton, director of the HOP program, explains the use of the colony counter in microbiology to a group of students during a laboratory session. Award of grants for Special Health Career Opportunity is made by the Bureau of Health Manpower Education of the National Institutes of Health. NIH is an agency of the U. S. Department of Health, Education, and Welfare. (NIH Photo #0-6 and 0-7)

EAST CHICAGO

EAST CHICAGO, IN--Dr. Edwin C. Marshall of the National Optometric Association demonstrates the measurement of the intraocular pressure (tonometry) to senior optometry student Marion Lewis during a routine eye examination. Support for Special Health Career Opportunity grants is administered by the Bureau of Health Manpower Education of the National Institutes of Health. NIH is an agency of the U. S. Department of Health, Education, and Welfare. (NIH Photo #O-8)

> *"Now I know that medicine is for me. I've just been an average student up to now, but only those with the patience, perseverance, determination and desire become the best doctors. My desire for this goal was rekindled."*

Reactions like these document the success of Livingston College's project to acquaint minority students with the health professions. Two innovative science development courses, intensive internship opportunities, and a visiting scientist program provided the information as well as the motivation to seek a career involving some aspect of medicine.

Since its opening in 1969 as a unit of Rutgers University, Livingston College has molded its approach to education to meet the needs of its student body, which is 25 percent Black and 7 percent Puerto Rican. Many of these students were admitted to Livingston on the basis of a subjective evaluation of their motivation and potential to succeed in college. Because of either financial difficulties or educationally disadvantaged backgrounds, these students achieved such poor grades and sub-average entrance examination scores that without special consideration, they probably would not have been accepted to an accredited institution of higher learning.

Realizing the potential to develop an interest among these students in a field with an inadequate representation of minority personnel, the Livingston faculty devised an interdisciplinary intensive approach to achieving this goal. Program Director Hannah Levin explains that "the purposes of the program were one, to motivate; and the other, to enrich or fill the gap between what these students need in order to succeed in college and what they actually gained from high school."

During the summer, the Albert Einstein College of Medicine of Yeshiva University, Bronx, New York, sponsored a group of interns from Livingston. This aspect of the program was the primary source of motivation for the participants because it provided the opportunity to work directly with health professionals on a day-to-day basis.

Under close supervision, the interns followed the same rigorous schedule as the professionals to whom they were assigned. They not only observed these professionals but actually assisted in performing basic health care functions. Dr. Levin feels that these "real-life experiences" are essential to bringing a student's medical career goals into perspective.

One of the science development courses provides a supplement in introductory biology. Its small faculty-to-student ratio and an extensive tutorial assistance arrangement make it possible to thoroughly prepare freshmen with a deficient background in basic science for the regular sophomore level courses.

For more advanced students, a new course in basic scientific thought integrates the study of society's health problems with fundamental scientific concepts. It first relates biology, chemistry and physics to one another and then applies an interdisciplinary approach to understanding the relationship of science and technology to man and society.

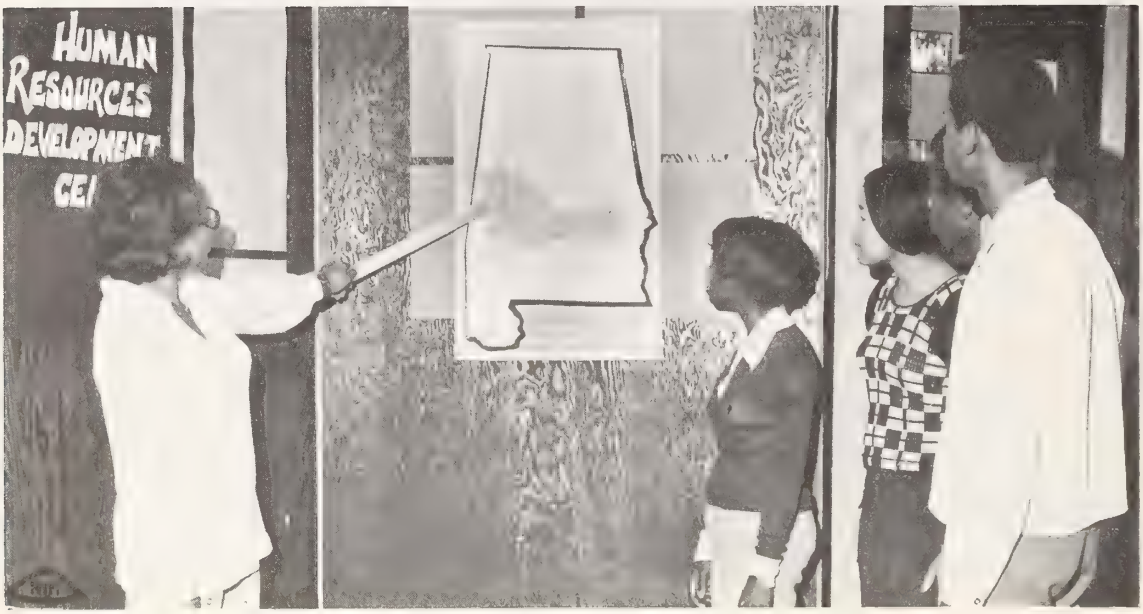
Field experience opportunities include a series of special courses in biology, psychology, community development, and ethnic studies in addition to placement in established community programs. This promotes an awareness of how mental disorders and emotional stress develop from various socio-economic, political, family, and biological factors and provides an opportunity to relate to these problems first-hand.

Finally, a Visiting Scientists Program will bring to Livingston outstanding minority health professionals from all over the world. The emphasis will be on small group interaction rather than a more formal presentation. A faculty member describes how these scientists' insights into how they overcame various obstacles to become successful might influence a student's perspective on his personal development:

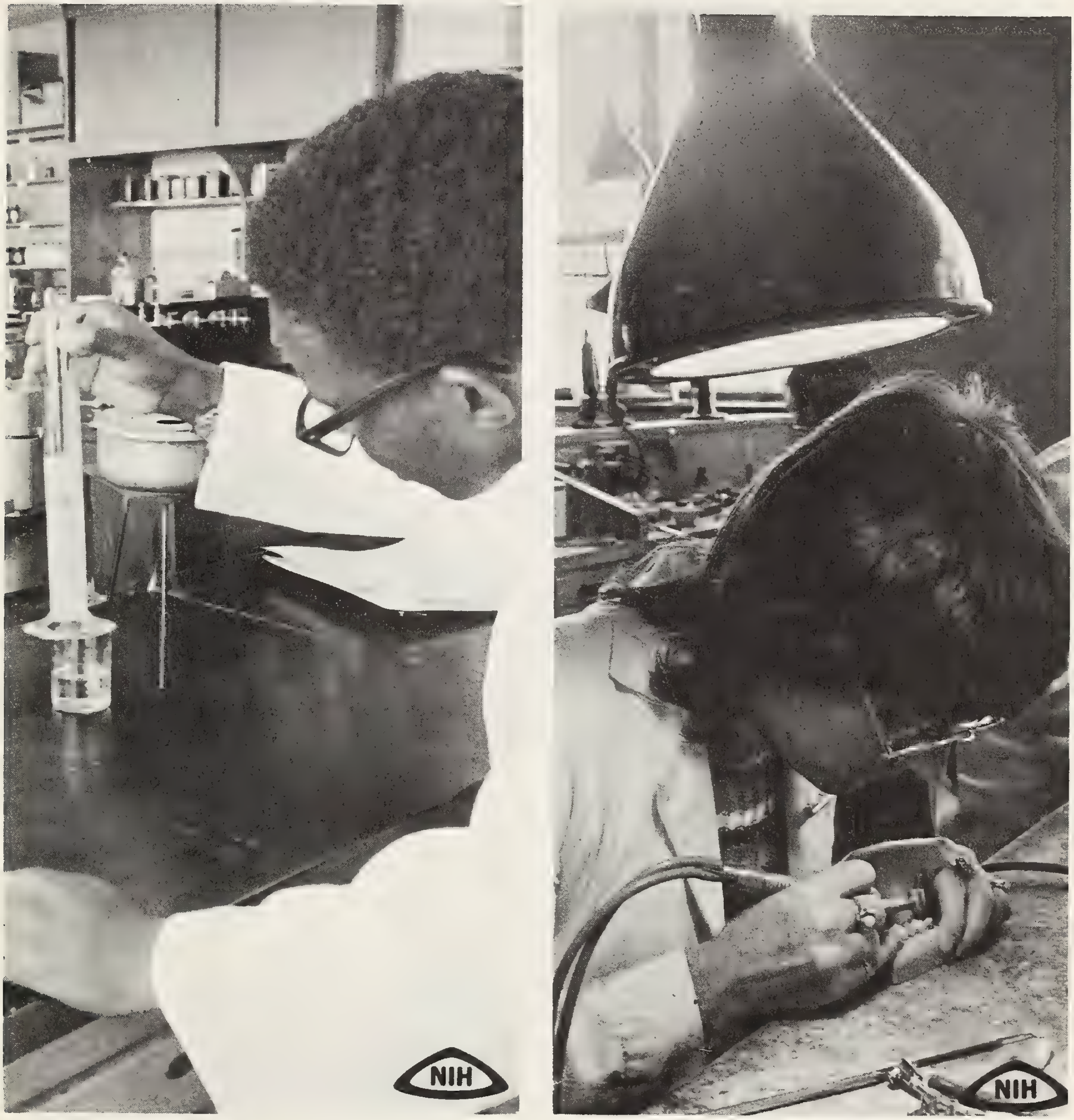
> *"What they are trying to do is to show these students that there are opportunities available for them, that they do have the expertise to participate in these programs, and that there are certain kinds of ideas and ideologies and ways of handling themselves that they have to get together not next year, but at this moment and at this time."*

NEW BRUNSWICK, NJ--At Albert Einstein College of Medicine of Yeshiva University, Bronx, New York, Richard Husbands checks the reading on an oxygen electrode. A participant in Livingston College's summer placement program, he worked in the hospital's department of biochemistry. Special Health Career Opportunity grants programs are supported by funds from the Bureau of Health Manpower Education, a component of the National Institutes of Health. NIH is an agency of the U. S. Department of Health, Education, and Welfare. (NIH Photo #O-9)

NEW BRUNSWICK, NJ--Livingston College student McLean Olson Gardiner watches Sandra Williams as she observes a culture through a microscope. Students also learn to operate more sophisticated scientific equipment, such as a preparative ultracentrifuge and a recording spectryolotometer, as part of their pre-med curriculum. The National Institutes of Health, through the Bureau of Health Manpower Education, administers the Special Health Career Opportunity grants. NIH is an agency of the U. S. Department of Health, Education, and Welfare. (NIH Photo #0-10)



TUSKEGEE INSTITUTE, AL--Beverly Holman discusses the minority recruitment and retention program at Tuskegee Institute with applicant Douglas Malone (upper photo). In lower photo, Mrs. Holman shows program participants Rachel Dixon, Pamela Pearson, Harold Robinson, and Samuel Raise potential locations for employment after completion of their education. Funds for Special Health Career Opportunity grants are administered by the Bureau of Health Manpower Education. BHME is a component of the National Institutes of Health, an agency of the U. S. Department of Health, Education, and Welfare.
(NIH Photo #0-11 and 0-12)



SAN FRANCISCO, CA--Two students at the University of California, San Francisco, practice skills that must be mastered before they can become professionals in their chosen fields. Both the School of Dentistry and the School of Pharmacy sponsor programs designed to interest minority students in medical careers. Special Health Career Opportunity grants are supported through the Bureau of Health Manpower Education. BHME is a component of HEW's National Institutes of Health. (NIH Photo #0-13 and 0-13a)

In 1968, the University of California at San Francisco expressed its concern with the lack of minority participation in the delivery of health care. The schools of medicine, dentistry, pharmacy, and nursing committed themselves to an eventual goal of 25 percent minority admissions for future incoming classes. The 25 percent figure was derived from census statistics showing that the population of the state of California includes 12 percent Chicanos, 10 percent Blacks, and 3 percent "others."

Both the School of Pharmacy and the School of Dentistry have developed minority recruitment and retention programs designed to meet the University's goal. Although many of the basic elements are similar, each school has tailored its program to meet its own standards and needs.

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Out of a total population of about 120,000 pharmacists in 1969, only 2,000 were Black. This low percentage of professional minority pharmacists is reflected in the composition of the School of Pharmacy's 1970 graduating class: 5 percent Blacks, 2 percent Mexican-Americans, and no American Indians.

The School of Pharmacy's program to improve these statistics begins with the identification of potential minority pharmacy students and follows these students throughout the admissions and educational processes. Recruitment teams canvass colleges with sizable minority populations, speaking to academic and social clubs and science classes.

The success of the recruitment program depends largely upon the enthusiasm generated by the teams. For that reason, minority students already enrolled in the School of Pharmacy assume the primary responsibility for recruitment activities. According to Project Director Robert D. Gibson, "We use our students as active recruiters to give the potential applicant someone on campus with whom he can identify--someone who had the chance to come to school and took advantage of that opportunity."

Community leaders, established minority health professionals, and school counselors cooperate in the School of Pharmacy's efforts to reach the potential minority pharmacy student. This "potential" is judged according to a broad standard for admission which considers all aspects of the individual applicant rather than relying on the traditional criteria of grades, test scores, and extracurricular activities.

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In the School of Dentistry, "We do what may not be unique now, but when we started it was fairly unique--trying to, as best we can, assess the potential performance of a student rather than the past performance," explains Project Director Robert Brigante.

A special admissions committee comprised of faculty, dentists from the minority community, and students in the program follows a set of guidelines designed for socio-economically disadvantaged applicants. As a supplement to the formal admissions process, minority students already in the program counsel those students they have recruited, assist them throughout the selection procedure, and teach them to score optimally on performance tests.

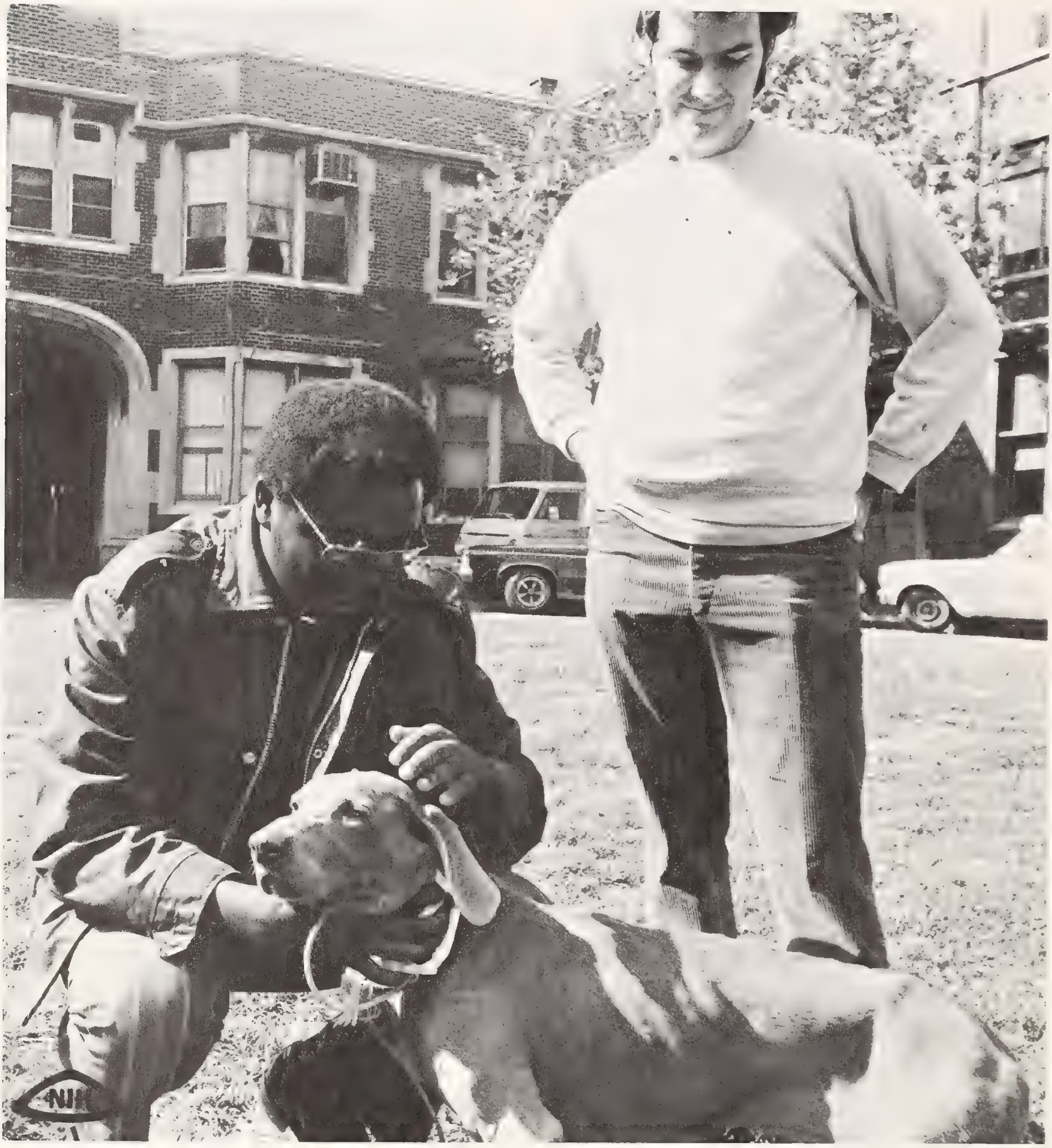
The actual admissions process includes an interview for every applicant. Interviews are conducted by one faculty member and a student with the same ethnic background as the applicant. The interview deals mainly with the subjective task of getting to know the applicant and deciding if his potential to succeed justifies admitting him ahead of another applicant whose grades and test scores may have been higher.

SAN FRANCISCO, CA--Two dental students at the University of California San Francisco's School of Dentistry work together, learning to properly drill and fill a cavity. The Bureau of Health Manpower Education has awarded grants for Special Health Career Opportunity programs. BHME is a component of the National Institutes of Health, an agency of the U. S. Department of Health, Education, and Welfare. (NIH Photo #0-14)

SAN FRANCISCO, CA--Dr. Mary Ellen Maycock, an instructor in the Department of Podiatric Biomechanics at California College of Podiatric Medicine, teaches students Lawrence Harkless and Lester Jones how to perform a biomechanical evaluation of the foot. In addition to clinical instruction, California College of Podiatric Medicine offers other types of training and support to help attract and retain minority students. The Special Health Career Opportunity grants are funded by the Bureau of Health Manpower Education of the National Institutes of Health. NIH is an agency of the U. S. Department of Health, Education, and Welfare. (NIH Photo #0-15)

BALTIMORE, MD--Before filling a prescription, Dolores Dixon, a student at the University of Maryland's School of Pharmacy (left photo), locates the patient's medication record in the pharmacy's file. In right photo, Alvin Johnson (right), an extern in the Professional Experience Program, checks charts in the University Hospital's pharmacy with his preceptor, Jack Mentzer. Funds from the Bureau of Health Manpower Education are awarded for the operation of Special Health Career Opportunity grants. BHME is a component of the National Institutes of Health, an agency of the U. S. Department of Health, Education, and Welfare. *(NIH Photo #O-16 and O-17)*

EL PASO, TX--El Paso Community College students Dawana Higgins and Eladio Valenzuela assist their instructor, Carolyn Patino, in setting up a film strip projector. Both students and instructors benefit from the use of audio-visual aids in medical education. The National Institutes of Health, through the Bureau of Health Manpower Education, supports programs organized under Special Health Career Opportunity grants. (NIH Photo #0-18)



PHILADELPHIA, PA--John Waller, a student preparing for entrance into the University of Pennsylvania's School of Veterinary Medicine, exercises a "patient" who is recovering from neck surgery at the veterinary hospital. Grant support of the Special Health Career Opportunity program is administered by the Bureau of Health Manpower Education of the National Institutes of Health. NIH is an agency of the U. S. Department of Health, Education, and Welfare. (NIH Photo #0-19)

PHILADELPHIA

Twelve students spent their summer at the University of Pennsylvania getting a first-hand look at the world of veterinary medicine. Through a program aimed at the recruitment and preparation of disadvantaged students for careers in veterinary medicine, these trainees combined classroom study, laboratory work, and a series of field trips and speakers in building a solid foundation for entering a school of veterinary medicine.

The idea for the program originated with the discovery that minority students often were not as well prepared as other applicants for admission to veterinary school. Last year the competition was so keen that the minority students might not have been admitted had they not received special consideration from the admissions committee.

To help these students and others with disadvantaged backgrounds get a good start toward a career in veterinary medicine, faculty from the School of Veterinary Medicine organized a summer program for a small group of students. Applicants who were rejected as well as those who were accepted for admission in September of 1972 participated along with a few "pre-vet" students.

"It gave me a sense of pride, and it intensified my motivations to become a vet," explained one trainee in his evaluation of the program. "It illustrated to me the vast need for black veterinarians."

The instructors reacted as favorably toward the program as the students they worked with. According to Program Director Dr. Dwight B. McNair Scott, "It's great fun for the faculty to deal with a small group on such a personal basis --to see them progress and learn and catch onto things, to see what their troubles are and where their hangups are and be able to deal with them. You worked with a student until you knew he understood."

Each of the course offerings--biochemistry, cell biology, anatomy, physiology, and genetics--was designed to introduce the students to the material they would encounter in their first year of veterinary school.

Two guest speakers and seven field trips supplemented the classroom study. The program's stress of the wide scope of the field of veterinary medicine was reflected in the choice of sites to visit: the Schuykill Nature Valley Reserve, Philadelphia Zoo Laboratories, the Pressure Chamber for Deep Sea Research at the Institute of Environmental Medicine, Cross Brothers Meat Inspection, the Philadelphia Rat Control Center, and the Westpark Animal Hospital.

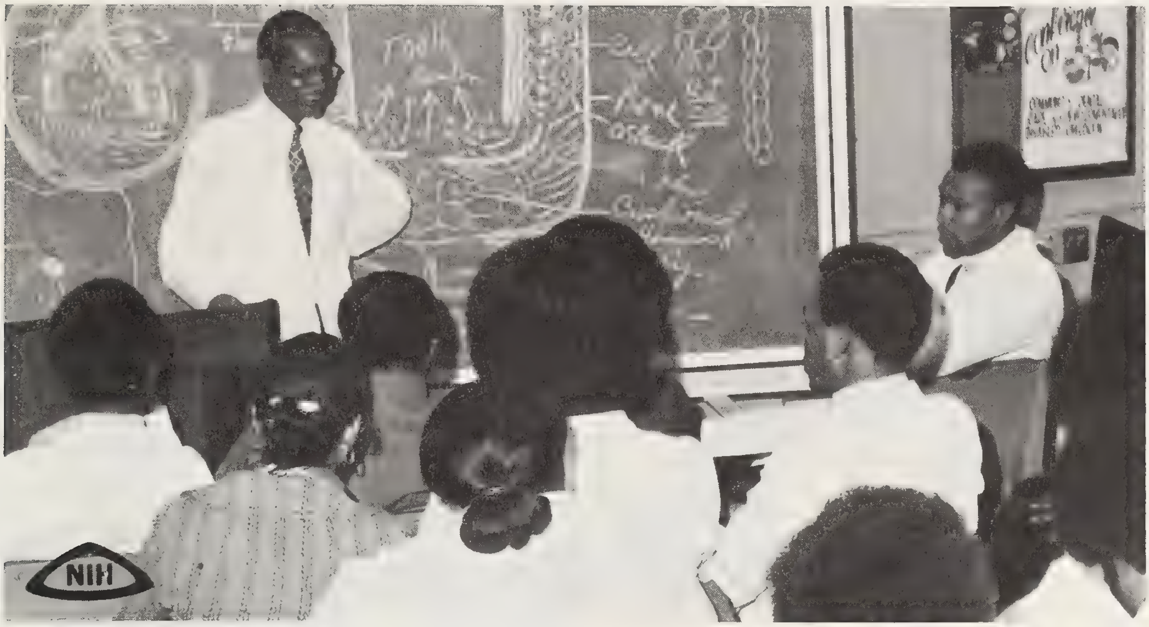
To round out the program, each student spent six hours a week--mostly at night and on weekends--in a small animal clinic, gaining experience in working with veterinarians. Next year's plans include clinic work at the New Bolton Center, a clinic for large animals located 32 miles southwest of the Philadelphia metropolitan campus.

Although it is still too early to determine if the program's participants are able to meet the challenge of veterinary school, Dr. Scott is confident that the special preparation provided by the program will increase a student's chance to succeed as well as encourage the admissions committee to admit more minority students in future semesters.

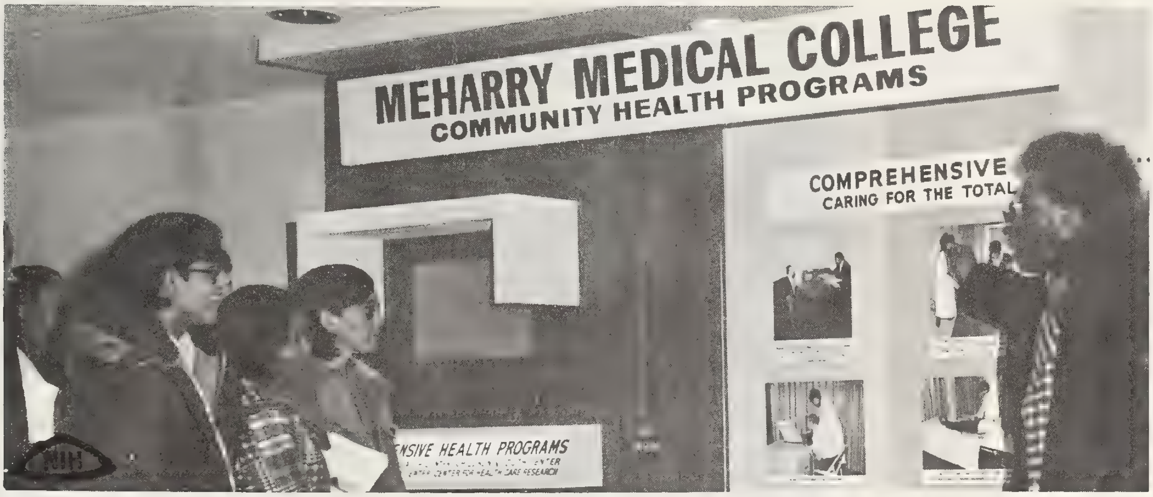
PHILADELPHIA, PA--Ken Johnson, co-director of the Anderson Science Institute, helps a member of a physical science class demonstrate the theory of vibrations (upper photo). In lower photo, students listen attentively as Bill Scruggs explains the processes of cloud formation and temperature change. Special Health Career Opportunity grants are funded by the Bureau of Health Manpower Education, a component of HEW's National Institutes of Health. (NIH Photo #0-20 and 0-21)

NEW ORLEANS, LA--Tulane University students Lydia Manuel and Bruce Butler attend a weekly seminar which is presented by a member of the faculty or administration to provide information on admissions, financial aid, curriculum, and ongoing clinical and basic scientific research. The National Institutes of Health, through the Bureau of Health Manpower Education, administers the Special Health Career Opportunity grants. NIH is an agency of the U. S. Department of Health, Education, and Welfare. (NIH Photo #O-22)

DULUTH, MN--The University of Minnesota, Duluth School of Medicine's "Native Americans into Medicine Program" exposes native American students to research and clinical experiences while providing supportive programs in the pre-medical curriculum for high school and college students. Don Olson (right) discusses a biochemistry lab experiment with co-director Dr. W. L. Salo. Special Health Career Opportunity grants are supported by funds from the Bureau of Health Manpower Education. BHME is a component of the National Institutes of Health, an agency of the U. S. Department of Health, Education, and Welfare. (NIH Photo #0-23)



WASHINGTON, DC--Narendar N. Soni, professor of histopathology at Howard University, lectures to a group of sophomore dental students. Dr. Soni directs the Academic Reinforcement Program in which these students participate. This program is funded through a Special Health Career Opportunity grant from the Bureau of Health Manpower Education. BHME is a component of the National Institutes of Health, an agency of the U. S. Department of Health, Education, and Welfare. (NIH Photo #O-24)



NASHVILLE, TN--Students of the Health Care Administration and Planning Program take a tour of one of Meharry Medical College's health facilities to broaden their understanding of their role in the health care delivery system. Guiding the tour (at right) are Deputy Director Willie Gable and Recruitment Counselor/ Planner Cheryl Holland. Special Health Career Opportunity grants are funded by the Bureau of Health Manpower Education, a component of HEW's National Institutes of Health. (NIH Photo #O-25)

NEWS&FEATURES FROM NIH
portfolio series

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE ■ Public Health Service ■ National Institutes of Health ■ Office of Information ■ Bethesda, Maryland 20014

SPECIAL HEALTH CAREER OPPORTUNITY GRANTS

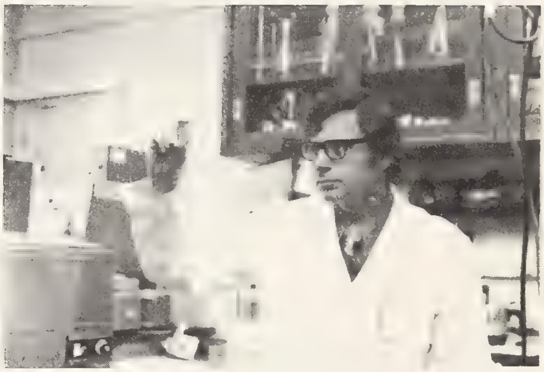
JANUARY 1973

NEWS&FEATURES FROM NIH

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE ▪ Public Health Service ▪ National Institutes of Health ▪ Office of Information ▪ Bethesda, Maryland 20014

February 10, 1973

SPECIAL SUPPLEMENT:
NIH Portfolio on Digestive Diseases



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NEWS & FEATURES From NIH February 10, 1973

Research Advances

HEAVY COFFEE CONSUMPTION LINKED TO HEART ATTACKS

People who drink more than five cups of coffee a day have about twice as great a risk of having an acute myocardial infarction as people who drink no coffee at all.

This finding of an association between coffee consumption and heart attacks emerges from the Boston Collaborative Drug Surveillance Program (BCDSP). The Program receives support through a contract from the National Institute of General Medical Sciences.

Hershel Jick, M.D. and Dennis Slone, M.D., co-directors of the BCDSP at Boston University Medical Center, collected data on the daily hot beverage intake before hospital admission of 276 patients with acute myocardial infarction. They compared this group to 1,104 matched control patients with other diseases. The investigators asked the patients if they drank zero, one to five, or more than five cups of coffee daily and similarly questioned them about tea consumption.

When they controlled the groups for age, sex, and hospital (patients were studied in eight different hospitals in the United States, Canada, Israel, and New Zealand), the investigators found no significant differences in tea consumption between the two groups. In fact, while heart attack patients consumed more coffee than their controls, the trend for tea consumption was in the opposite direction. Tea consumption was greater in non-U.S. hospitals, but separate examination of the data from American and from non-American hospitals provided no evidence of any consistent

(more)

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(more)

association between tea drinking and heart attack.

Association between coffee ingestion and acute myocardial infarction was present in males and females, in young (up to 59 years old) and old (60 years or older), and in American hospitals and non-American hospitals. The association held in those patients with and those without diabetes or hypertension.

Although Drs. Jick and Slone found a strong correlation between coffee drinking and cigarette smoking, this finding could not explain the association between coffee drinking and heart attack. Only a small excess of smokers were in the group that had heart attacks.

Drs. Jick and Slone offer several possible explanations for their findings.

According to them, "A first possibility is that patients who drink coffee heavily and patients who develop myocardial infarction have similar personalities and thus coffee drinking would only be indirectly related to myocardial infarctions." Although they have no information for or against this theory, the investigators believe it remains a possible explanation.

A second possibility is that "there is a substance or substances in coffee other than caffeine that makes individuals who drink coffee heavily more susceptible to developing myocardial infarction." The investigators rule out caffeine and sugar as explanations, since tea drinkers consume similar quantities of both substances but no substantial relationships were found between heart attacks and tea.

(more)

Coffee (Cont'd)

Other possible explanations include differences in the patients' diets and past histories of myocardial infarction. It is possible that patients with previous attacks of the disease could have increased their consumption of coffee as a reaction to the stress of having had a heart attack. However, since no information was available concerning the number of study patients experiencing previous myocardial infarction, this possibility remains to be explored further.

The BCDSP is continuing its study of the observed association of coffee drinking with heart attacks. A larger study of about 600 patients will be completed within two months and will include additional pieces of information concerning sugar intake with coffee and tea, past history of myocardial infarction, and patient occupations.

Drs. Jick and Slone report their findings in *Lancet*, December 16, 1972.

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NOTE TO SCIENCE WRITERS: For background on the Boston Collaborative Drug Surveillance Program and a photo of Drs. Jick and Slone, see the Medical News Tip, *page 16.*

Self-Application...

TOPICAL FLUORIDE GEL INHIBITS DENTAL CARIES

Fluoridation of the public water supply is generally accepted as the most effective and least expensive method of reducing dental caries. However, in areas where the population is not exposed to fluoridated water, topical fluoride applications represent another effective method of reducing dental caries.

A three-year study in Mississippi of the effect of self-applied acidulated phosphate fluoride agents on dental caries produced data to support this procedure. According to Aaron Trubman, DDS, and James A. Crellin, DDS, of the Mississippi State Board of Health, 618 third grade children (average age 8.07 years) participated throughout the entire course of the study. All were lifelong residents of Mississippi communities having little or no concentration of fluoride in their water supplies.

All children were given a base-line visual dental examination in order to record the number of carious lesions, fillings, and missing teeth. They were then randomly assigned to one of four groups, taking into account age, sex, race, and caries history:

Group 1: brushed with a *nonfluoride* prophylaxis paste
applied a *nonfluoride* gel

Group 2: brushed with a *fluoride* paste
applied a *nonfluoride* gel

Group 3: brushed with a *nonfluoride* prophylaxis paste
applied a *fluoride* gel

Group 4: brushed with a *fluoride* prophylaxis paste
applied a *fluoride* gel

(more)

The children brushed their teeth with the assigned paste, rinsed, and then placed flexible trays filled with the assigned gel over their teeth for four minutes. Dental hygienists supervised the treatment of groups of 60 to 70 children, with the assistance of teachers and parents. The procedures were conducted four times during the school year, with about two months between sessions. The children received annual examinations during the study.

According to Drs. Trubman and Crellin, the study findings reveal "a significant inhibitory caries effect on both teeth and surfaces from the use of fluoride gel, but no significant effect attributable to the use of the fluoride paste either in combination with nonfluoride or fluoride gels." School schildren in the study using the fluoride gel exhibited caries increments in teeth and surfaces ranging from 22.1% to 24.8% *less* than children whose teeth were treated with the nonfluoride gel.

The investigators add that although repeated exposure to acidulated phosphate fluoride gel resulted in decreased caries increments, the study did not determine how long the build-up of fluoride in the enamel will afford protection.

This finding of lower increments of caries after self-application of fluoride gel was noted after the second and third years of the study, but not after the first. The investigators concluded that the maximum beneficial effect of the fluoride gel, when applied four times a year, was reached after two years.

(more)

Fluoride Gel (Cont'd)

When the dentists examined shed deciduous teeth, they found that the teeth from the group treated with the fluoride gel exhibited higher concentrations of fluoride than those from the fluoride paste group or from the control group. Even though teeth receiving fluoride paste contained more fluoride than teeth from the control group, the use of paste did not result in protection against caries. Drs. Trubman and Crellin believe that this finding suggests that a certain level of fluoride is required before significant protection is achieved.

Since professional application of topical fluoride is not feasible for most public dental health programs due to its cost and the limited availability of dental manpower, self-application of an acidulated phosphate fluoride gel appears to offer a good method of delivering the inhibitory effects of fluoride to children.

Drs. Trubman and Crellin report their findings in the *Journal of the American Dental Association*, January 1973. Their study was supported in part by a grant from the NIH Division of Dental Health.

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Research Advances

IN THE LITERATURE:
Proceedings of the National Academy of Sciences, August 1972
Journal of Immunology, August 1972

SCIENTISTS DEVELOP METHOD FOR STUDYING IMMUNE RESPONSES--A new method of studying the immune responses of certain white blood cells to viral infections has been developed by scientists at the National Institute of Dental Research (NIDR). Their findings should prove helpful in the diagnosis of viral disorders.

The test is specific in that it not only differentiates between viruses, but even between two closely related strains. The technique can also indicate within a few days of exposure to a virus whether or not sensitization has taken place and whether the immune reaction is strong or weak.

The investigators first used the test to compare the reactions of rabbit lymphocytes to herpes simplex virus (the cause of fever blisters) and to vaccinia virus (the cause of cowpox and the basis of human vaccination against smallpox). Later, they used the method to distinguish between types 1 and 2 of herpes simplex virus. Type 1 usually affects only the mouth region, while type 2 is generally a genital infection.

In these latter experiments, the investigators tested leukocytes from rabbits sensitized with either type 1 or type 2 herpes simplex virus against inactivated viruses of both strains. In response to cross-reacting antigens in both strains, these cells reacted somewhat, but the degree of stimulation was more than twice as great with the strain to which they were originally sensitized, reflecting stronger response to type-specific antigens. In this way it should be possible to decide which strain of a virus is the

(more)

infectious agent in certain diseases.

Drs. Gary L. Rosenberg, Charles Wohlenberg, and Abner L. Notkins of NIDR; Andre J. Nahmias of Emory University, Atlanta, Georgia, and Paul A. Farber of Temple University, Philadelphia, Pennsylvania, participated in the research.

#

Photo Feature

NIH DENTAL SCIENTIST STUDIES ORIGIN OF BACTERIAL DISEASES

National Institute of Dental Research (NIDR) studies of evolution among bacteria--the oldest forms of life--may one day explain the origin of all bacterial disease, not just those of dental importance. Dr. Jack London of the Institute is working to explain how disease-causing types of bacteria develop from free-living relatives which still live on earth in simple substances like water, nitrogen, carbon-dioxide, sulfur, and iron.

Traditionally, scientists have based evolutionary studies of plants and animals on similarities of form. But the simple shapes of bacteria seem to have little to do with their relationship since some of the fossil remains in rocks two to three billion years old are bacterial outlines identical to modern, free-living sulfur and iron bacteria.

Usually bacteriologists classify microorganisms according to whether or not they accept the Gram stain. Regardless of size or shape, blue-black Gram positive bacteria are entirely different from Gram negative bacteria that stain red. Next, these scientists look at growth habits.

Dr. London believes that enzyme molecules (which are always proteins) can be much better genealogic and evolutionary indicators than growth differences. Pigs, baboons, and man eat similar foods and produce many similar metabolic products, but their relationships do not depend on such factors, he explains.

The best known evolutionary molecule in animals is DNA which codes for hereditary traits, but it evolves too rapidly for use in broad bacterial

(more)

studies. A suitable molecule for bacterial studies would be any enzyme which performs an essential function in a wide variety of organisms. When large chunks of such a molecule are exactly alike in different species, the similarity indicates that the molecule developed in the most primitive form and has been "conserved" over the ages. Presumably, the more alike such molecules are in different species, the more closely the species are related.

Dr. London suggests that small essential enzymes, particularly those under similar control systems in several species, are the molecules most likely to show evolutionary relationships. A large protein that controls a simple reaction could mutate and survive more easily than a small molecule which catalyzes an essential, more complicated reaction.

According to the NIDR scientist, only two species of mouth bacteria grow on malate, a salt of malic acid found in many fruits. One of these associated with tooth decay is *Lactobacillus casei*, a rod-shaped form. The other, *Streptococcus faecalis*, is spherical and generally lives harmlessly in the intestine, although some strains can cause abscessed teeth and rheumatic heart disease.

Dr. London compared malic enzymes from 10 strains of *S. faecalis* and 18 strains of *L. casei*. Purified enzymes from each of the *S. faecalis* strains moved through a plastic gel at the same rate, showing that the molecules were similar in size and electric charge. Malic enzymes from the *L. casei* strains differed. Further comparisons of the three groups showed that portions of the molecules must be identical because antibodies made separately

(more)

cross-reacted to some degree with the others.

Another of Dr. London's molecular tools is the aldolase enzyme, which splits compound sugars and releases energy for all bacteria which make lactic acid as a digestive waste. This protein enables him to group these bacteria according to family lines. He can demonstrate which lines have produced only harmless human passengers and which have developed some dangerous "piratical" members.

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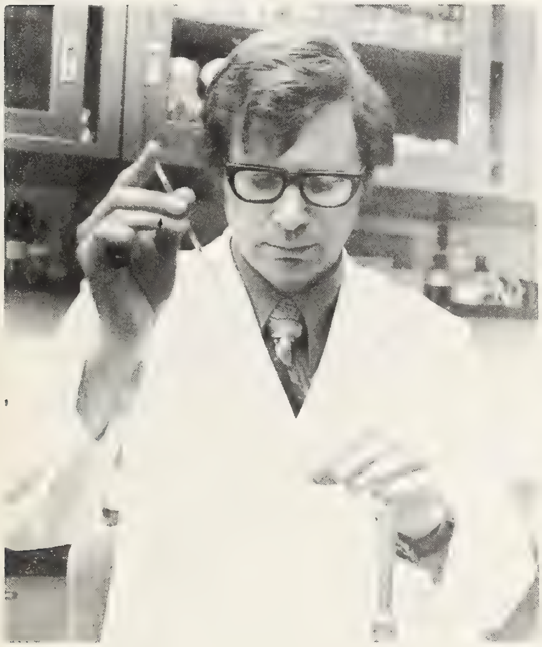
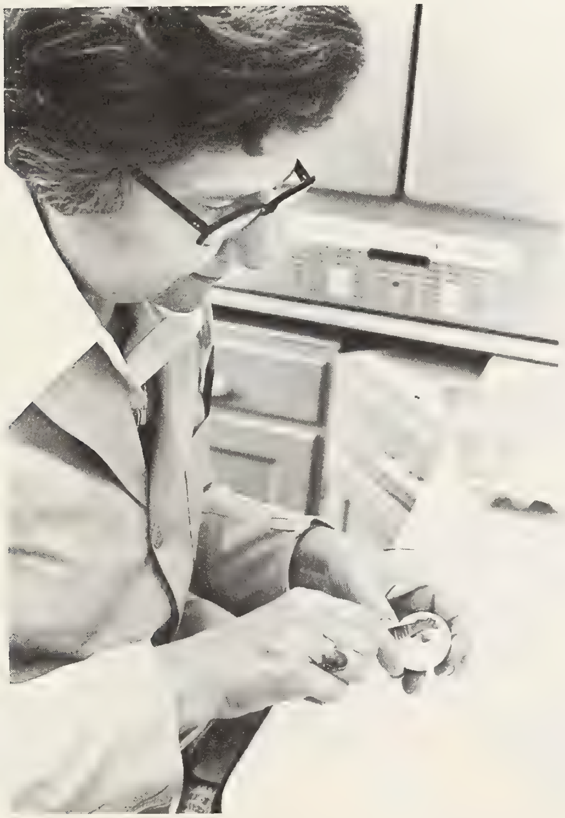


In his laboratory at the National Institute of Dental Research, Dr. Jack London is shown transferring (above) streptococci cultures for preparation of protein extracts, performing electrophoresis (top right) on protein extracts, and (bottom right) helping Kimberly Kline purify proteins for electrophoresis. (NIH Photo #996, 997, 998)

Photo Feature

Grantees at Northwestern...

RESEARCHERS EXPLORE THE BASIC SCIENCES



NIH-funded research at the Northwestern University Medical School involves various areas of the biomedical sciences. Clockwise from top, left: Maria Bernik, M.D., analyzes a microcinematographic sequence of human kidney cells. A grantee of the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD), Dr. Bernik's work may lead to prevention and treatment of blood clots. Paula Stern, Ph.D., also a NIAMDD grantee, injects a tracer amount of radioactive calcium into a rat. Her research may explain why women develop brittle bones in later life. Mary Faith Orr, Ph.D., removes a chick embryo from an egg for study of the structures of the inner ear. Dr. Orr's study, supported by the National Institute of Neurological Diseases and Stroke, could contribute to an understanding of the causes of diseases of the inner ear. (NIH Photos #999, 1000, 1001)

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Photo Feature

Grantees Participate...

ALLERGY ACADEMY TO HEAR DISCUSSIONS OF RESEARCH

Scientific communication is an important aspect of the research on allergic diseases which is supported by the National Institute of Allergy and Infectious Diseases (NIAID).

Among the investigators giving talks at the American Academy of Allergy 29th Annual Meeting (February 10 to 14) are several whose work is supported by NIH grants.

Elliott Middleton, Jr., M.D., who is President of the Academy, directs the NIAID Allergic Disease Center at Children's Asthma Research Institute and Hospital (CARIH), Denver. In addition to his Presidential Address, he will discuss the effect of hydrocortisone on antigenic histamine release in human leukocytes.

(more)

CARIH's Dr. Middleton (left) and associates analyze research data.

Allergy Academy (Cont'd)

The Academy's President-elect, Charles E. Reed, M.D., heads the NIAID Allergic Research Center at the University of Wisconsin, Madison. His topic is "Adverse Reactions to Immunotherapy with Alternaria."

Dr. Philip S. Norman, the Academy's Treasurer, will discuss "Specific IgE Antibody Measurement in the Diagnosis of Ragweed Hay Fever." He is director of the NIAID Allergic Disease Center at the Johns Hopkins University School of Medicine, Baltimore.

Another speaker is the head of the NIAID Allergic Disease Center at the State University of New York, Buffalo. He is Dr. Carl Arbesman who will lecture on "Immunoglobulin E In Sera That Contain Precipitins to Aspergillus."

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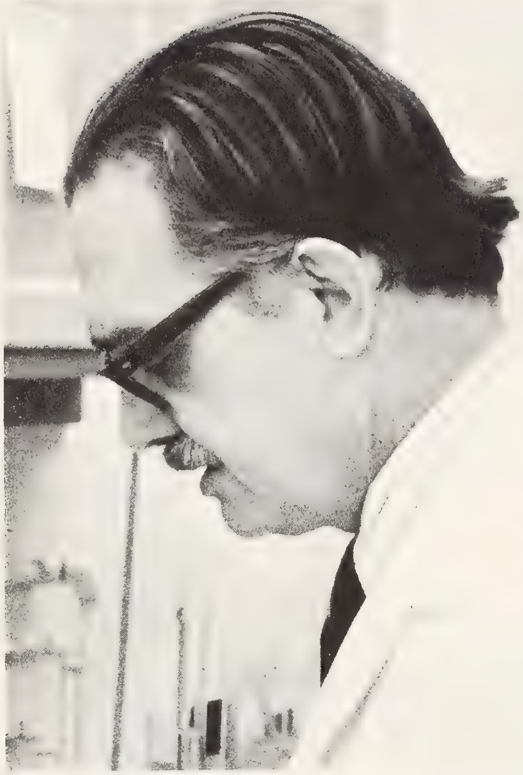
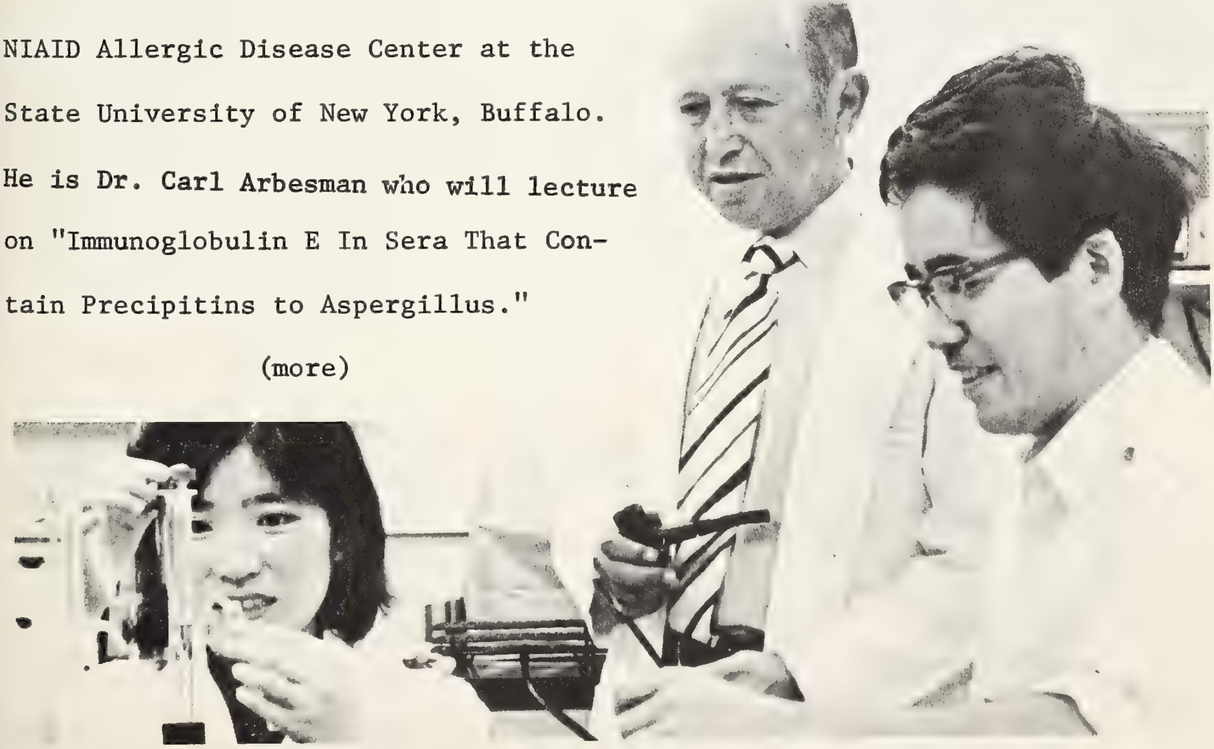


Madison's Dr. Reed (above) and Buffalo's Dr. Arbesman (below holding pipe).



Allergy Academy (Cont'd)

Participating in the Academy's Postgraduate Program sessions are K. Frank Austen, M.D., and Alfred Steinberg, M.D. Dr. Austen heads the NIAID Allergic Disease Center at Robert B. Brigham Hospital, Boston, while Dr. Steinberg is Senior Investigator, Arthritis and Rheumatism Branch, National Institute of Arthritis, Metabolism, and Digestive Diseases.

Research at NIAID's Allergic Disease Centers includes clinical studies (primarily on an outpatient basis), laboratory experiments, and investigations involving animals. The investigators are concerned with immunologic factors, respiratory infections in asthma, and various pharmacologic, environmental, and psychologic variables which contribute to asthma symptoms.

EDITOR'S NOTE: The NIAID Centers will be featured in a coming supplement to NEWS & FEATURES From NIH *entitled "The NIH Portfolio on Allergic Disease Centers."*

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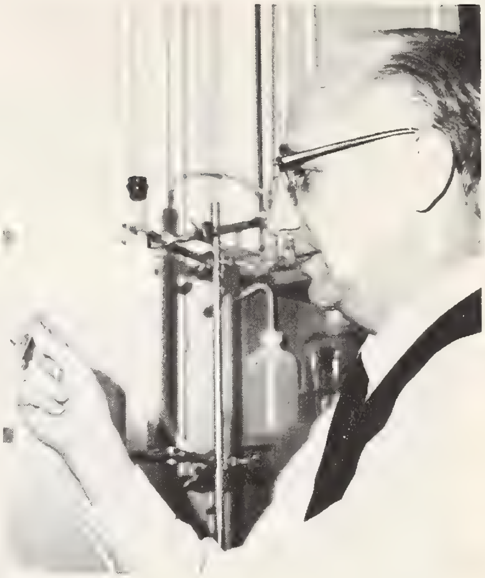

Boston's Dr. Austen (above) and NIAMDD's Dr. Steinberg (below).

Medical News Tip

BOSTON PROGRAM PROVIDES INFORMATION ON VARIOUS MEDICATION--The Boston Collaborative Drug Surveillance Program (BCDSP) of the Boston University Medical Center is a comprehensive effort that obtains information on the therapeutic and adverse effects of commonly used medications.

Dr. Hershel Jick (left) and Dr. Dennis Slone are co-directors of the Boston Collaborative Drug Surveillance Program. Staff members of the program represent the disciplines of clinical pharmacology, epidemiology, computer sciences, and biostatistics. (NIH Photo #1002)

Established in 1966, the BCDSP operates through a complex organization that collects, processes, computerizes, and analyzes data from hospitals in the United States, Canada, New Zealand, and Israel. Most of the support for the program derives from a contract with the National Institute of General Medical Sciences (NIGMS).

Using trained observers who interview patients and their physicians and examine hospital records, the program has gathered data on about 15,000 individuals hospitalized at the participating institutions. The data are then subjected to extensive analysis to identify new or unusual hypothesis concerning relationships between drugs and adverse effects of drugs and patients characteristics and diseases.

For additional information about the BCDSP, contact: NIGMS Information Office, Bldg. 31, Room 4A-46, NIH, Bethesda, Md. 20014. Phone (301) 496-5676.

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New Publication:
Blood Level Determinations of Antiepileptic Drugs --Clinical Value and Methods

To help scientists and physicians use the gas-liquid chromotography (GLC) services which are being provided by numerous laboratories, the National Institute of Neurological Diseases and Stroke (NINDS) has published *Blood Level Determinations of Antiepileptic Drugs--Clinical Value and Methods*, a bibliography with Key-Word and author indexes.

The adaptation of gas-liquid chromotography (GLC) to measure levels of antiepileptic drugs in the blood of patients taking them has greatly improved epilepsy management. Now the physician can pinpoint precisely the dose which gives the drug blood level that is controlling an epilepsy case. Moreover, the doctor can tell whether the patient is taking his prescribed medicines, and whether he is taking other drugs at the same time.

In drug treatment of epilepsy it is the amount of drug in the patient's body that counts not the size of the dose he takes. For a long time it was not possible to find out how much of a drug stayed in a patient's blood. The result was often under- or over-medication which either did not control seizures or caused unpleasant side effects. This happened because some persons metabolize, absorb, and excrete the same drug at different rates than others.

For a copy of this publication, contact: Information Office, NINDS, Building 31, Room 8A-03, NIH, Bethesda, MD 20014, Phone: (301) 496-5751.

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NEWS&FEATURES FROM NIH

PORTFOLIO · DIGESTIVE DISEASES

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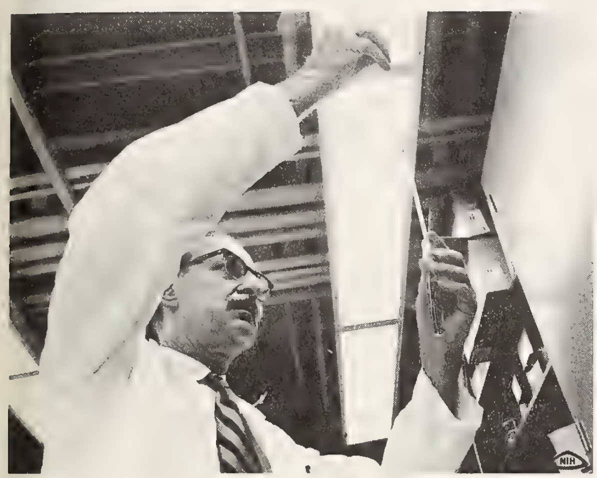
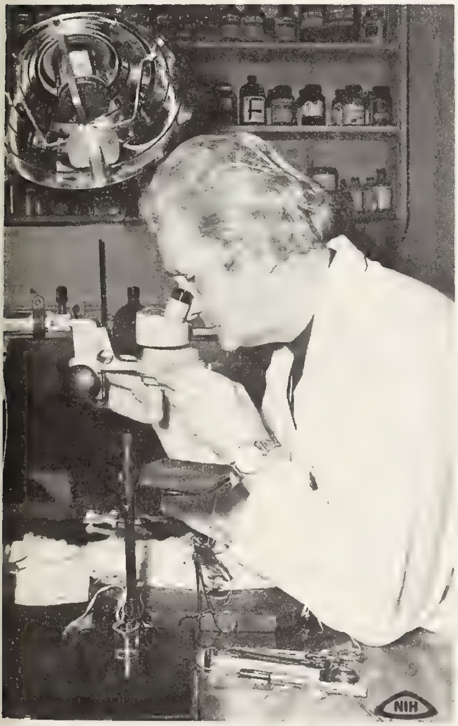
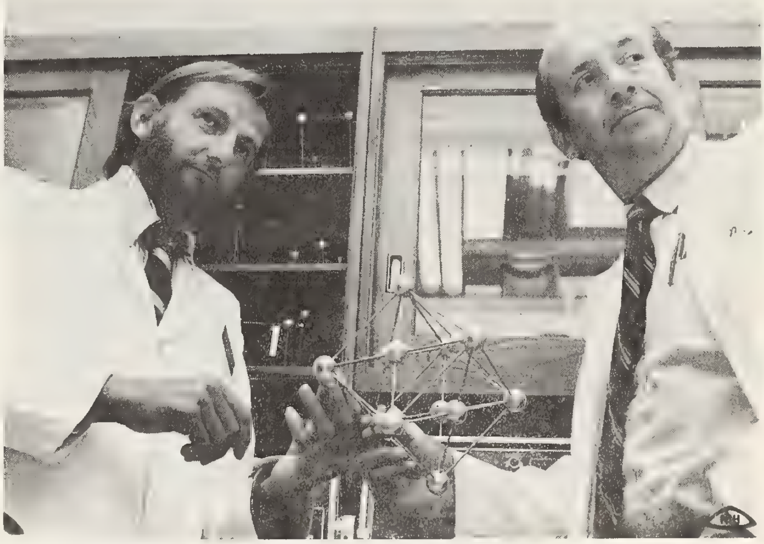






NEWS & FEATURES From NIH
Marc Stern, Editor, [301] 496-1206
Carol M. Sussman, Associate Editor

INTRODUCTION: NIAMDD SUPPORTS DIGESTIVE DISEASE RESEARCH

The National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) bears the responsibility for the Federal Government's program of research in the field of digestive diseases. This Institute was first established in 1948 under the name of Experimental Biology and Medicine Institute and assembled together many NIH laboratories involved in relatively fundamental studies in endocrinology, metabolism, biochemistry, pathology, nutrition, and physiology.

Digestive diseases include disorders of the stomach, intestines, biliary passages, liver, and pancreas. The major digestive diseases are peptic ulcer, hepatitis, cirrhosis of the liver, gallstones, infectious diarrhea, ileitis, ulcerative colitis, cancer of the colon and rectum, and malabsorption. The causes are various infection, cancer, alcoholism, genetic defects, and reactions to life stress.

Although many ailments involving the gastrointestinal tract are poorly understood, they are among the most common illnesses in the country, ranking second only to diseases of the heart and circulation in the number of physician office visits or house calls. Peptic ulcer or peptic ulcer symptoms will strike about 10 percent of all adults in the United States at some time in their lives. Diseases of the stomach and intestines may afflict persons of any age, but most often affect those in the middle-aged groups at the peak of their most vigorous and productive periods, often causing prolonged and expensive hospitalization and countless social and emotional problems. Some diseases such as ulcerative colitis are of a chronic nature. Many patients are afflicted for years with this disorder and may have to undergo extensive and repeated treatments and surgery.

Digestive diseases constitute a health problem of great magnitude. Using several national indices, the fact emerges that one out of every six illnesses in our population arises primarily from diseases of the digestive tract. The National Center for Health Statistics of the Health Services and Mental Health Administration has found that nearly 13 million Americans have chronic digestive diseases; such conditions together constitute the number one reason for hospitalization in this country, exceeding in frequency all forms of heart disease and all forms of accidents. Moreover, of all 705,000 patients discharged from Veterans Hospitals in fiscal year 1970, almost 27 percent had suffered from gastrointestinal conditions, and in half of these it was the principal diagnosis.

Of all the causes of disability due to illness in our country, digestive diseases rank second. Over two million Americans are impaired in some degree by the disease; of these 1.2 million are limited in performing useful work and 400,000 are totally disabled. Among the employed, digestive diseases each day account for 200,000 absentees from work due to illness, making it the leading cause of lost time from work among male employees. Almost 140,000 veterans receive payments for service connected disability due to gastrointestinal conditions, at a cost to the nation approximating 100 million dollars per year.

(more)

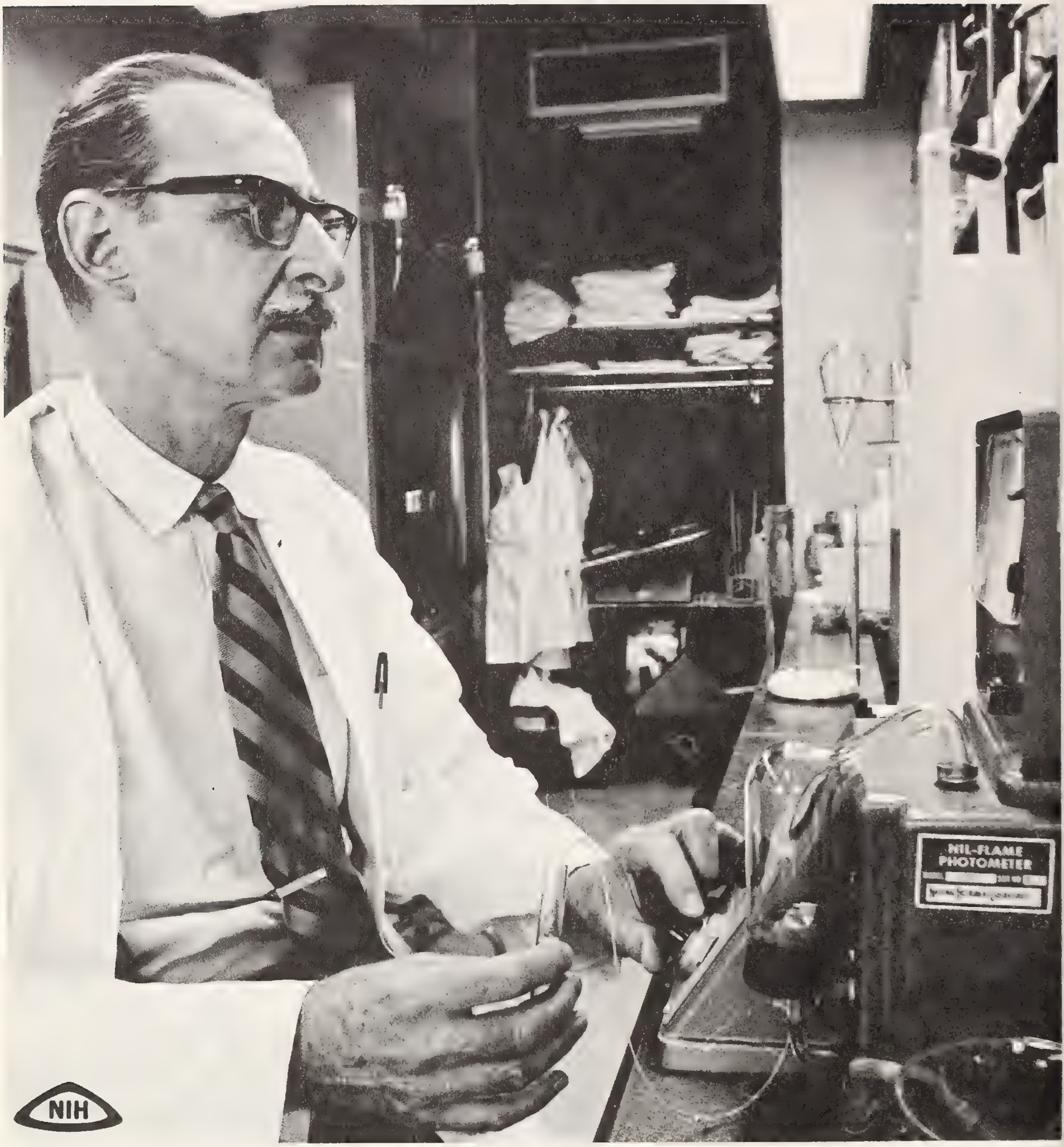
INTRODUCTION

The diseases of the digestive tract include several of the most common forms of internal cancer, which account for about 30 percent of all deaths from cancer. These and other diseases of the digestive system together produce the fourth largest death toll among the population of the United States.

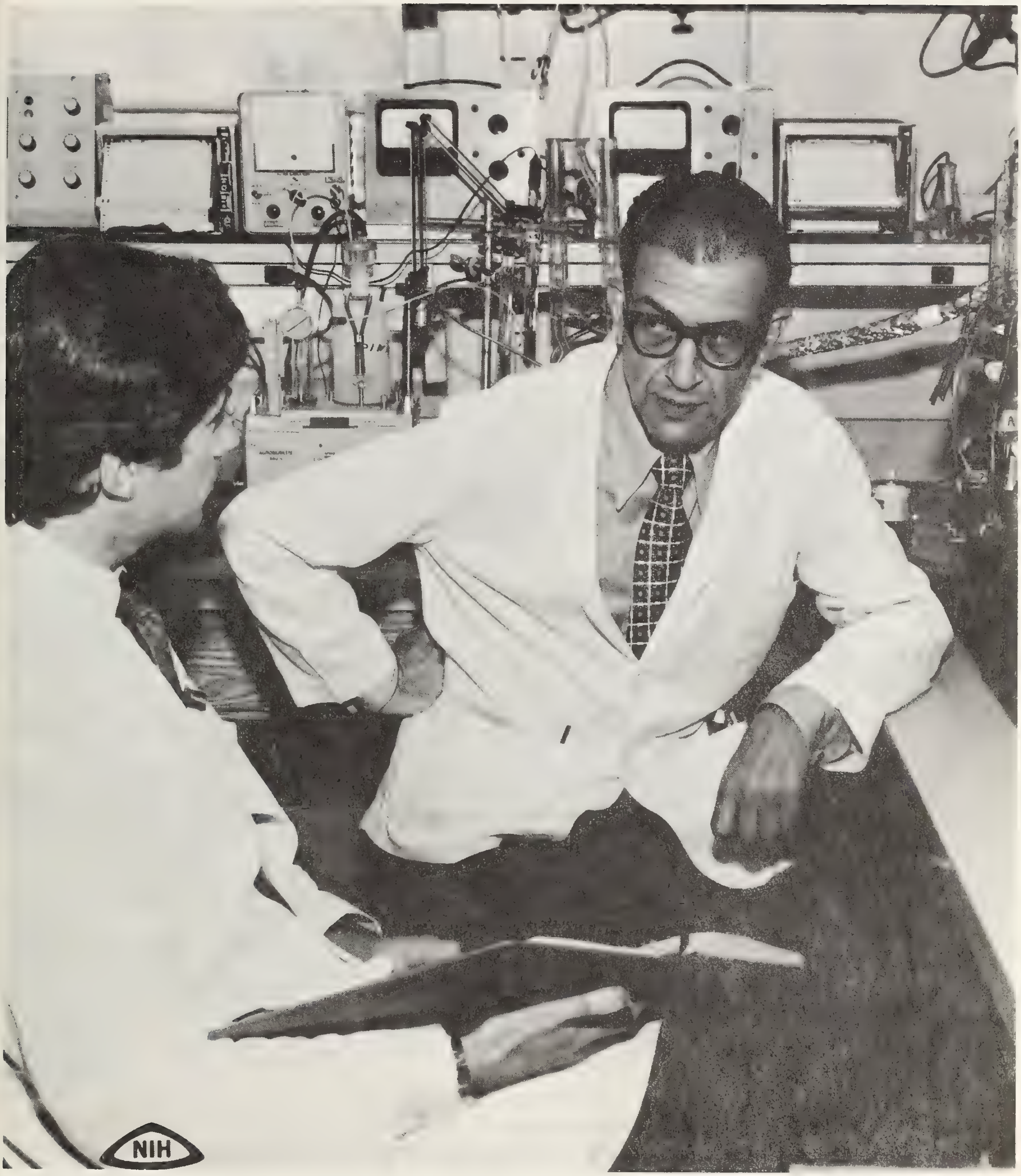
In a health problem of this magnitude, characterized by significantly high mortality rates in the middle years of life, the social disruptions are obvious, but this impact can best be measured in economic terms. When calculated by the United States Public Health Service in 1963, the total cost of illness resulting from digestive disease was approximately eight billion dollars per year, or one percent of the gross national product. It may reasonably be assumed that the figure presently approaches 10 billion dollars per year. The cost of medical care for digestive diseases is high, in part because of the costs of surgical operations for conditions not now curable by medical means. The stomach is operated upon for gastric ulcer, and the colon is removed for ulcerative colitis; the cost of gall bladder surgery alone runs to over half a billion dollars a year in the United States. Such figures include not only the cost of medical care but also the loss of income due to absence from work and the loss of income from death prior to the age of 65. By these criteria, digestive diseases rank third among all categories of diseases as a cause of economic loss.

EDITOR'S NOTE: *This Introduction was prepared by George Kitzes, Ph.D., who is Digestive Diseases Program Director, and by Sarah C. Kalser, Ph.D., who is Digestive Diseases Associate Program Director. The National Institute of Arthritis, Metabolism, and Digestive Diseases is a component of the National Institutes of Health, an agency of the U. S. Department of Health, Education, and Welfare.*

This Portfolio illustrates work being performed by some of the scientists who are conducting NIH-supported research on the problem of digestive diseases.

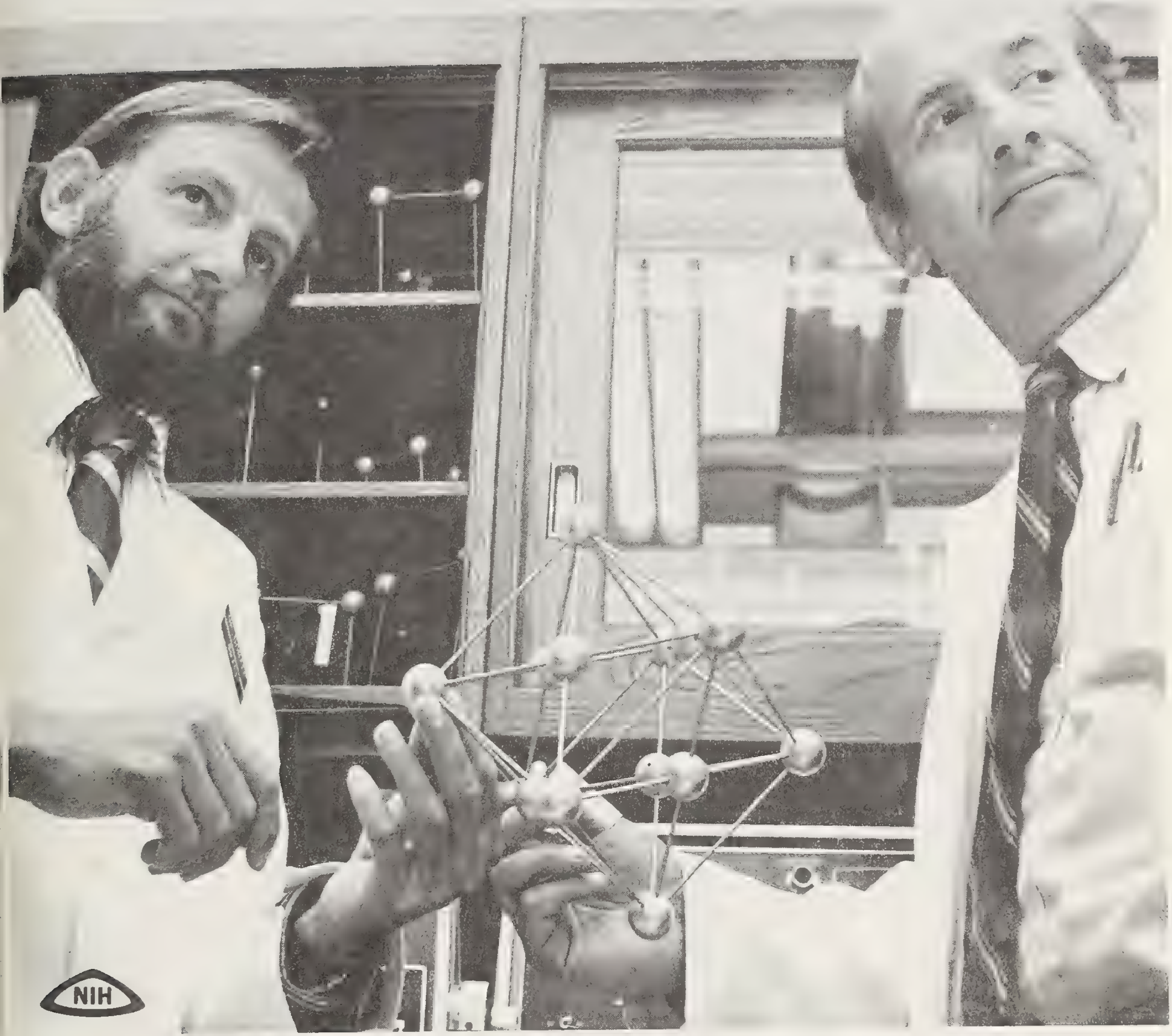


ANN ARBOR, MI--The concentration of sodium and potassium in gastric juices is measured in a flame photometer by Dr. Horace W. Davenport, Ph.D., University of Michigan Professor and Chairman of Physiology. Research into the problem of digestive diseases is supported by the National Institute of Arthritis, Metabolism, and Digestive Diseases. ***(NIH Photo #D-1)***

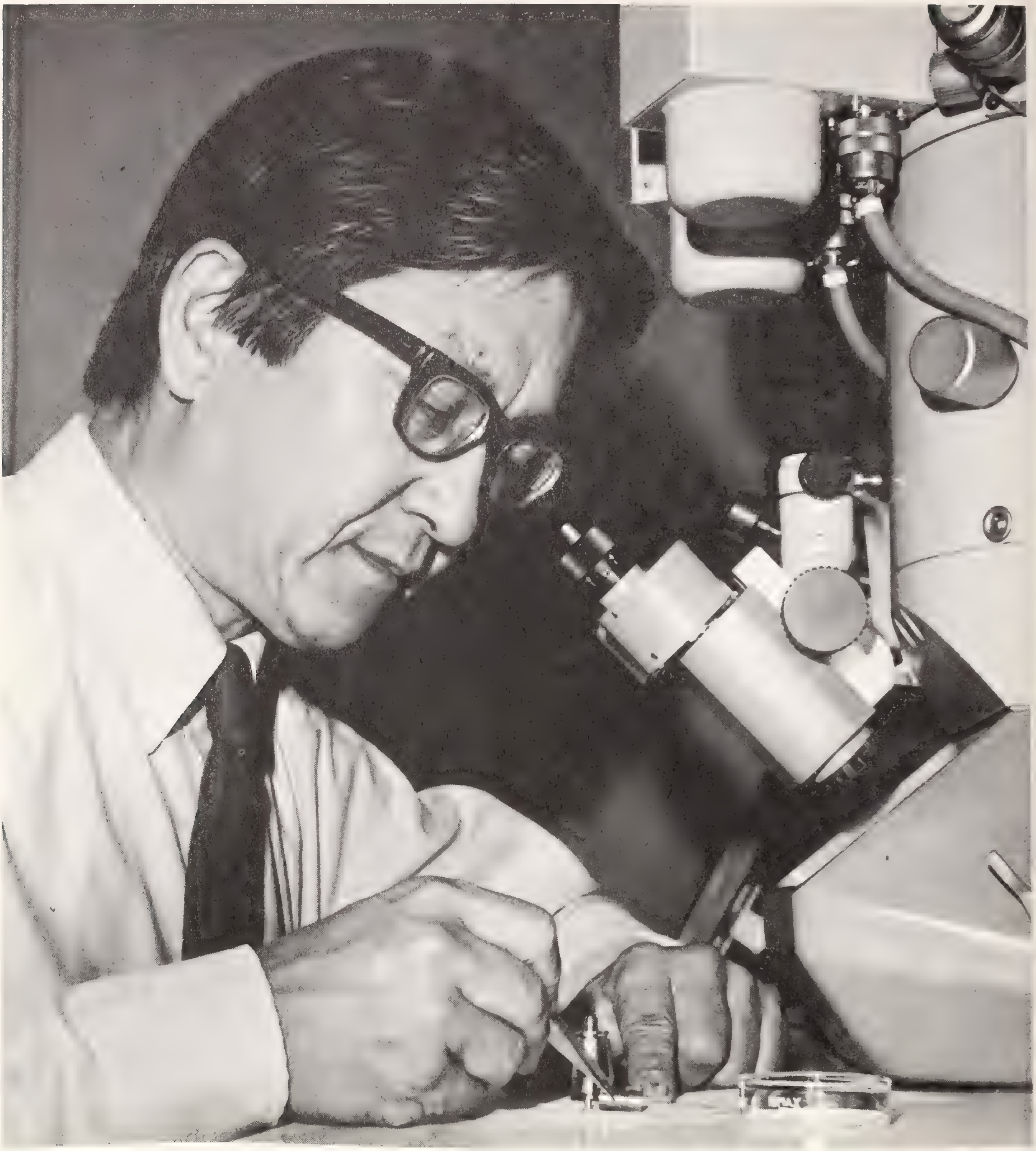


BOSTON, MA--In Beth Israel Hospital's Department of Surgery, Dr. William Silen is conducting research on gastric ulcer disease. Digestive diseases research is funded by the National Institute of Arthritis, Metabolism, and Digestive Diseases. (NIH Photo #D-2)

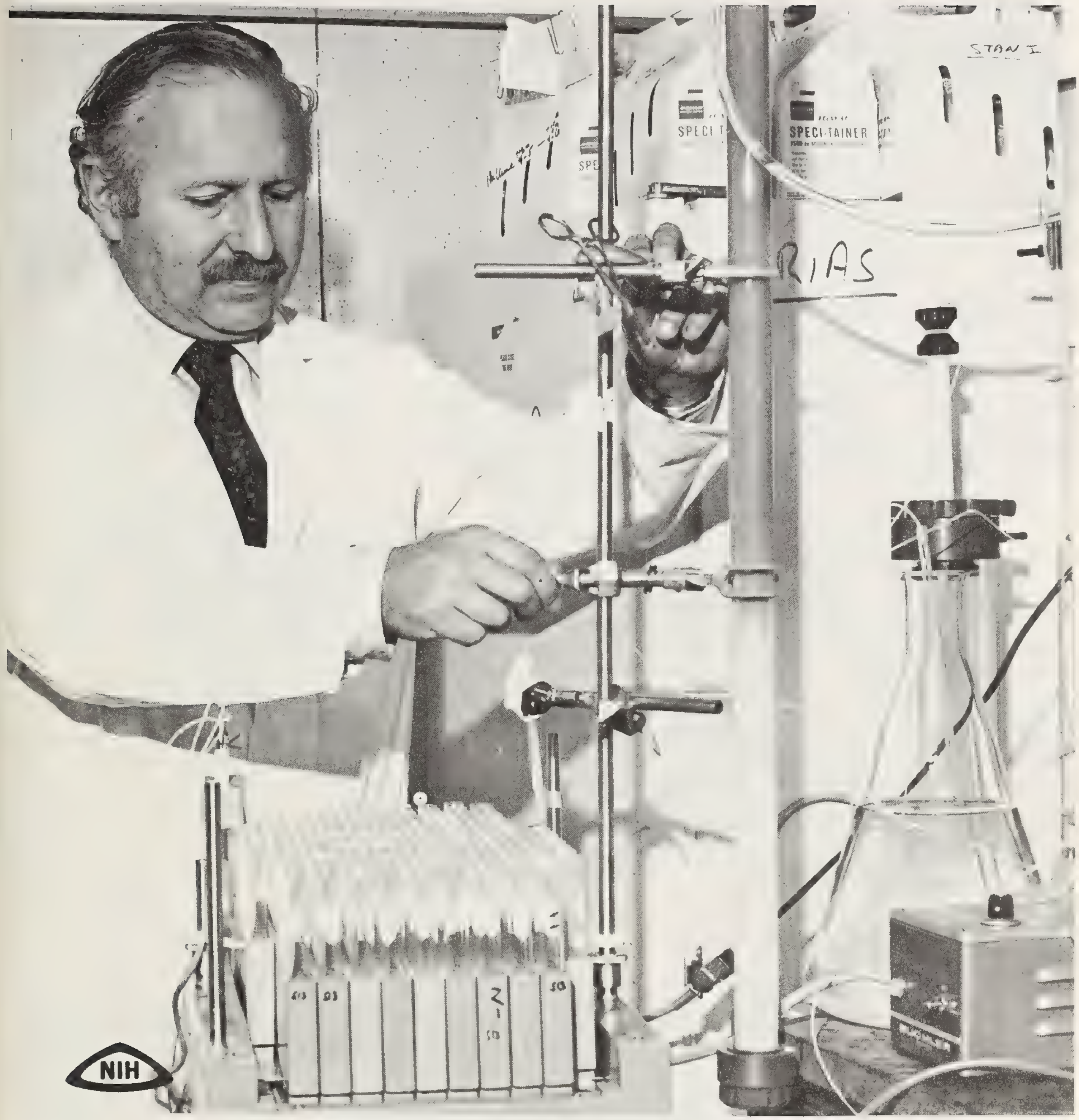
BOSTON, MA--Using an electron microscope, Drs. Jerry S. Trier (seated) and Lauran D. Harris, both associate professors of medicine at Boston University School of Medicine, correlate the structure of human intestinal and stomach tissues with their function in normal individuals and patients with diseases of the gastrointestinal tract. An NIH component, the National Institute of Arthritis, Metabolism, and Digestive Diseases, administers research into the problem of digestive diseases. (NIH Photo #D-3)



BOSTON, MA--Examining a model which illustrates one type of crystalline structure are Dr. Donald M. Small (left), associate professor of medicine, and Dr. Robert M. Donaldson, Jr., professor of medicine, at Boston University Medical Center. The research team at Boston University is particularly concerned with understanding normal and abnormal gastrointestinal and hepatic functions in terms of molecular structure. The National Institute of Arthritis, Metabolism, and Digestive Diseases administers the NIH-funded research program into the problem of digestive diseases. (NIH Photo #D-4)

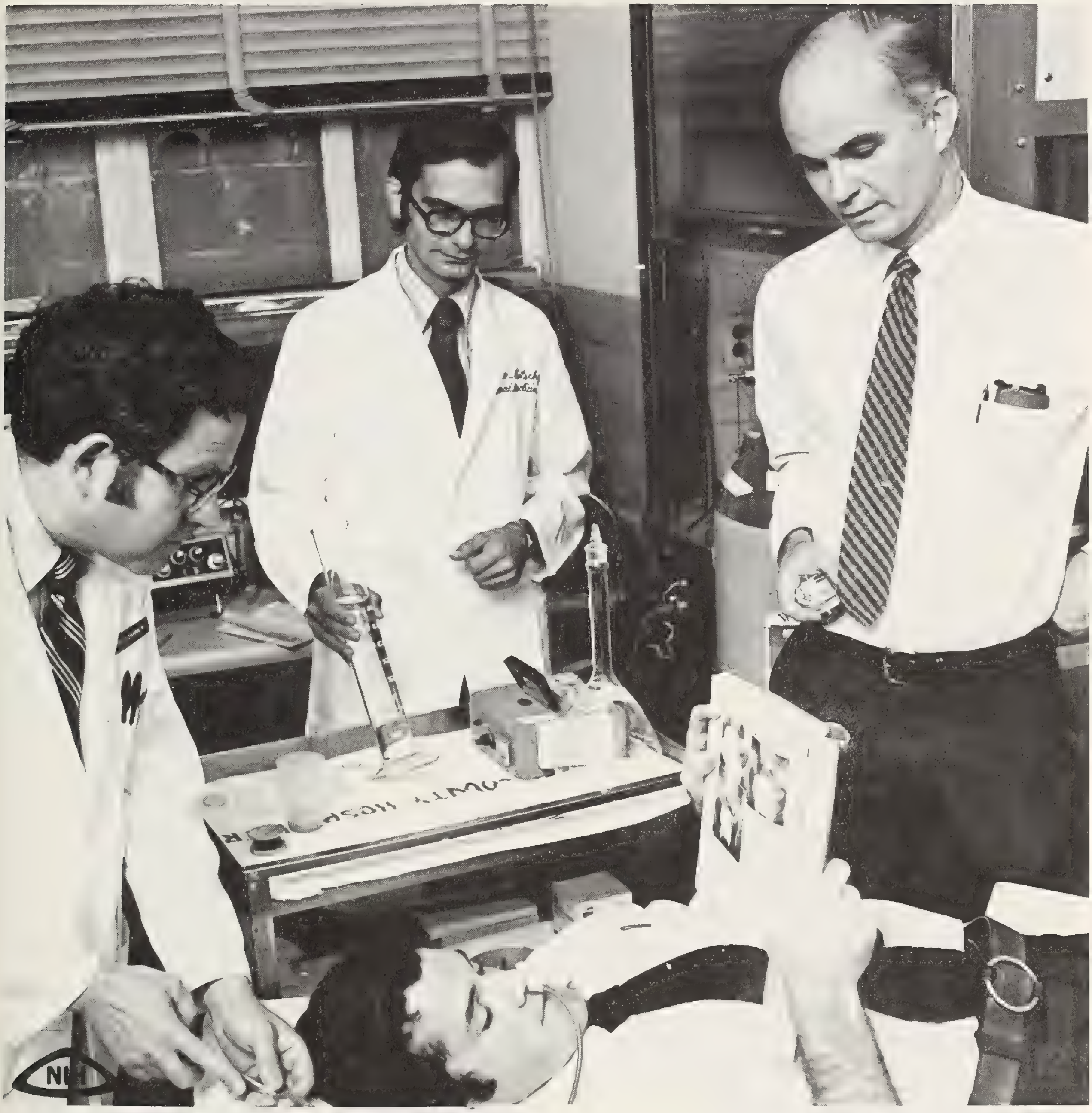


*BOSTON, MA--At Harvard Medical School, Susumu Ito, Ph.D., is studying the **ultrastructure** of tissues obtained from normal and diseased organs of the gastrointestinal tract to elucidate the causative mechanisms of digestive diseases. Funds for research into digestive diseases are administered by the National Institute of Arthritis, Metabolism, and Digestive Diseases. (NIH Photo #D-5)*



BRONX, NY--Irwin M. Arias, M.D., is conducting research on the basic mechanisms of liver function and metabolism to better understand the underlying deficiencies or defects accounting for certain genetic diseases related to the liver. His digestive diseases research in the Department of Medicine of Albert Einstein College of Medicine of Yeshiva University is supported by NIH's National Institute of Arthritis, Metabolism, and Digestive Diseases. (NIH Photo #D-6)

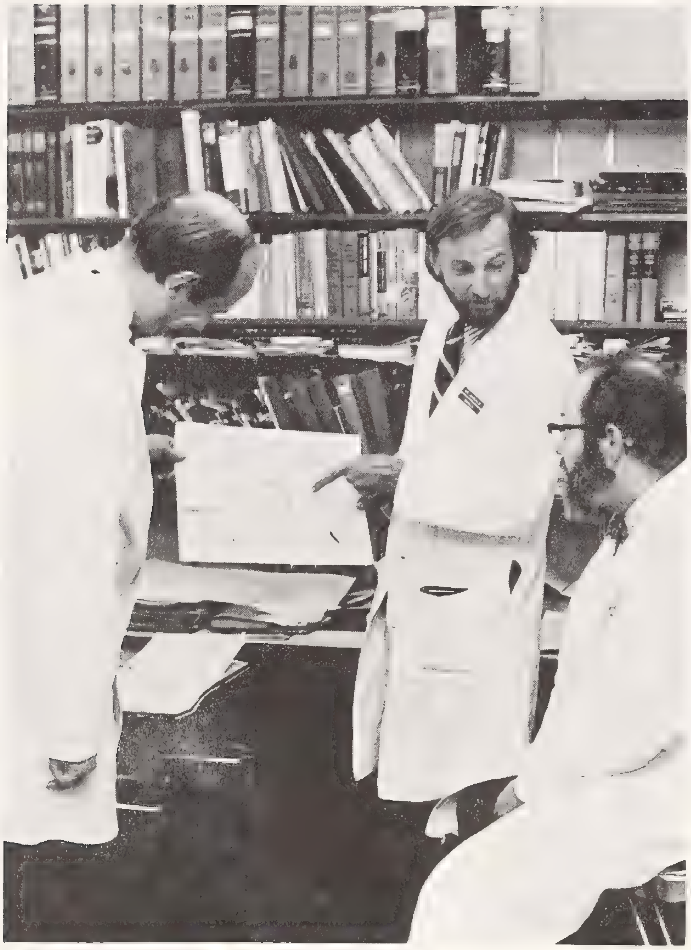
CHAPEL HILL, NC--Eszter B. Kokas, M.D., is shown at the University of North Carolina studying the physiology of the small intestine with a special emphasis on the intestinal hormone villikinin. The National Institute of Arthritis, Metabolism, and Digestive Diseases supports her research into the problem of digestive diseases. (NIH Photo #D-7)

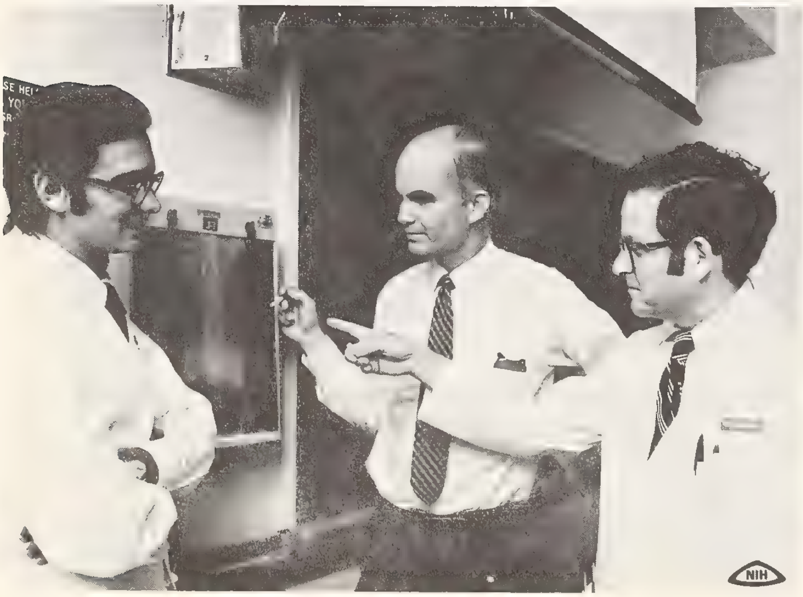


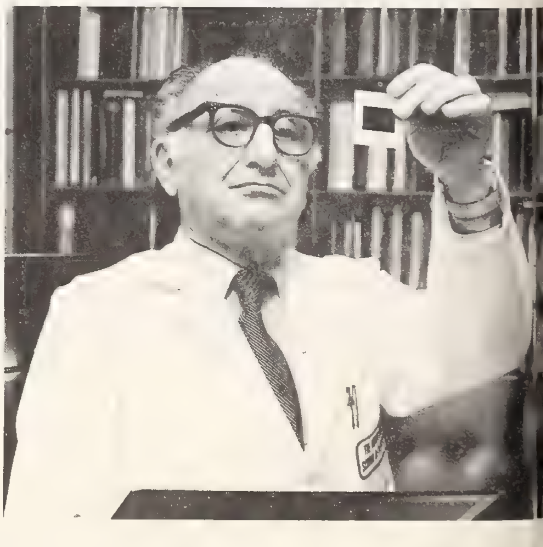
DALLAS, TX--Dr. Burton Combes (left) checks on student volunteer Bryan Murphy during tests in the gastroenterology lab at Parkland Memorial Hospital which are part of long-range studies of the mechanics of intestinal absorption being conducted at The University of Texas Southwestern Medical School. Looking on are two other faculty researchers, Dr. John M. Dietschy (center) and Dr. John S. Fordtran. Drs. Combes, Dietschy, and Fordtran all are professors of internal medicine at Southwestern. Murphy is wasting no time: He is continuing to study a medical textbook as the test proceeds. An NIH component, the National Institute of Arthritis, Metabolism, and Digestive Diseases, administers research into the problem of digestive diseases. (NIH Photo #D-8)

DURHAM, NC--Dr. Malcolm P. Tyor, Chief of the Division of Gastroenterology at Duke University Medical Center, is shown examining a print-out from a spectrophotometer which tells the concentration of bile acids in his study of digestive diseases in relation to bile acid metabolism. Research into the problem of digestive diseases is supported by the National Institute of Arthritis, Metabolism, and Digestive Diseases. (NIH Photo #D-9)

EAST ORANGE, NJ--Dr. Carroll M. Leevy is studying liver disease resulting from alcoholism and malnutrition at the New Jersey College of Medicine. His laboratory is in the Division of Hepatic Metabolism and Nutrition. Digestive disease research is funded by the National Institute of Arthritis, Metabolism, and Digestive Diseases. (NIH Photo #D-10)







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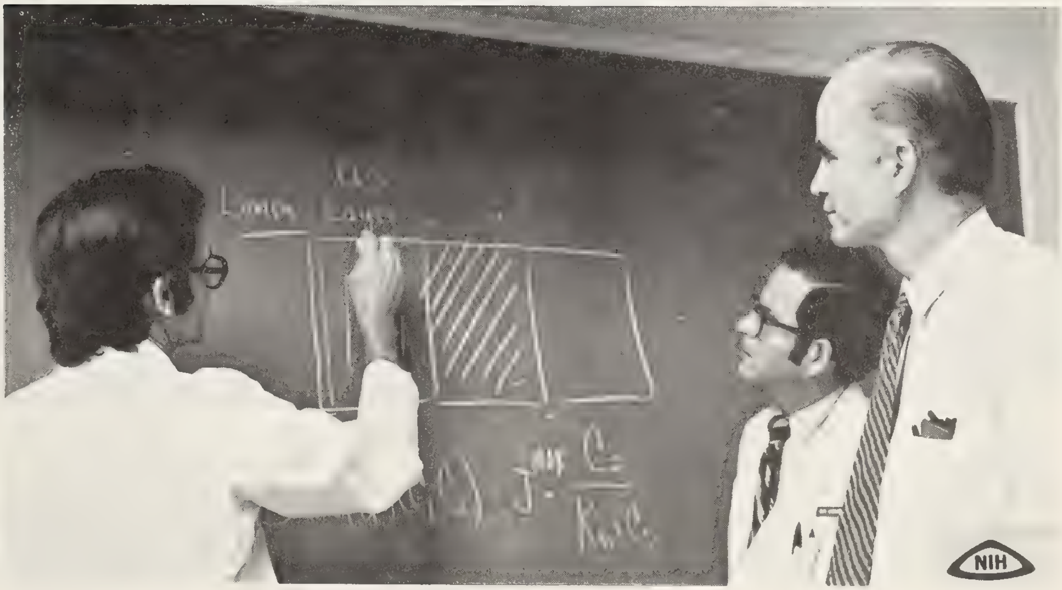

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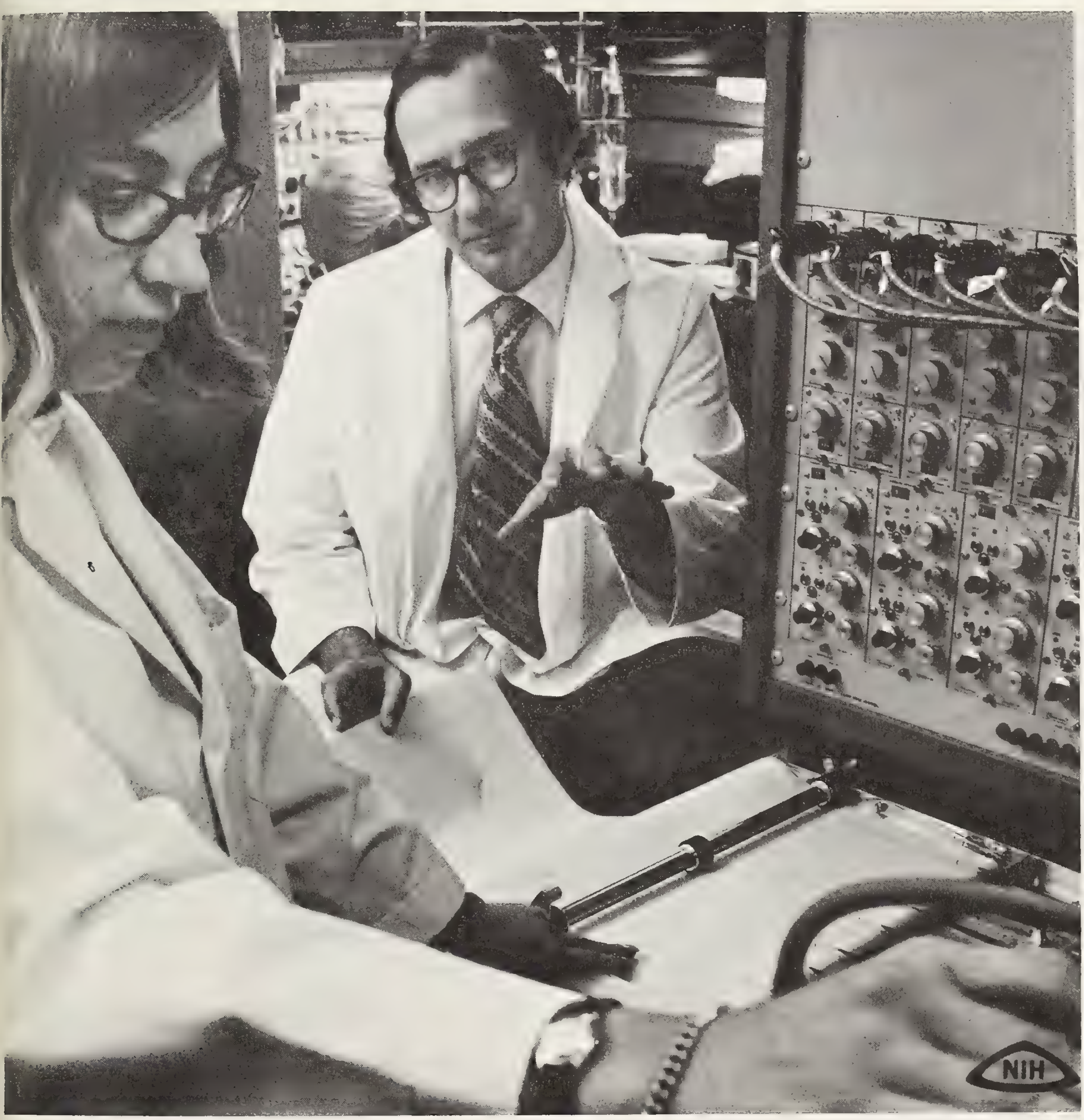
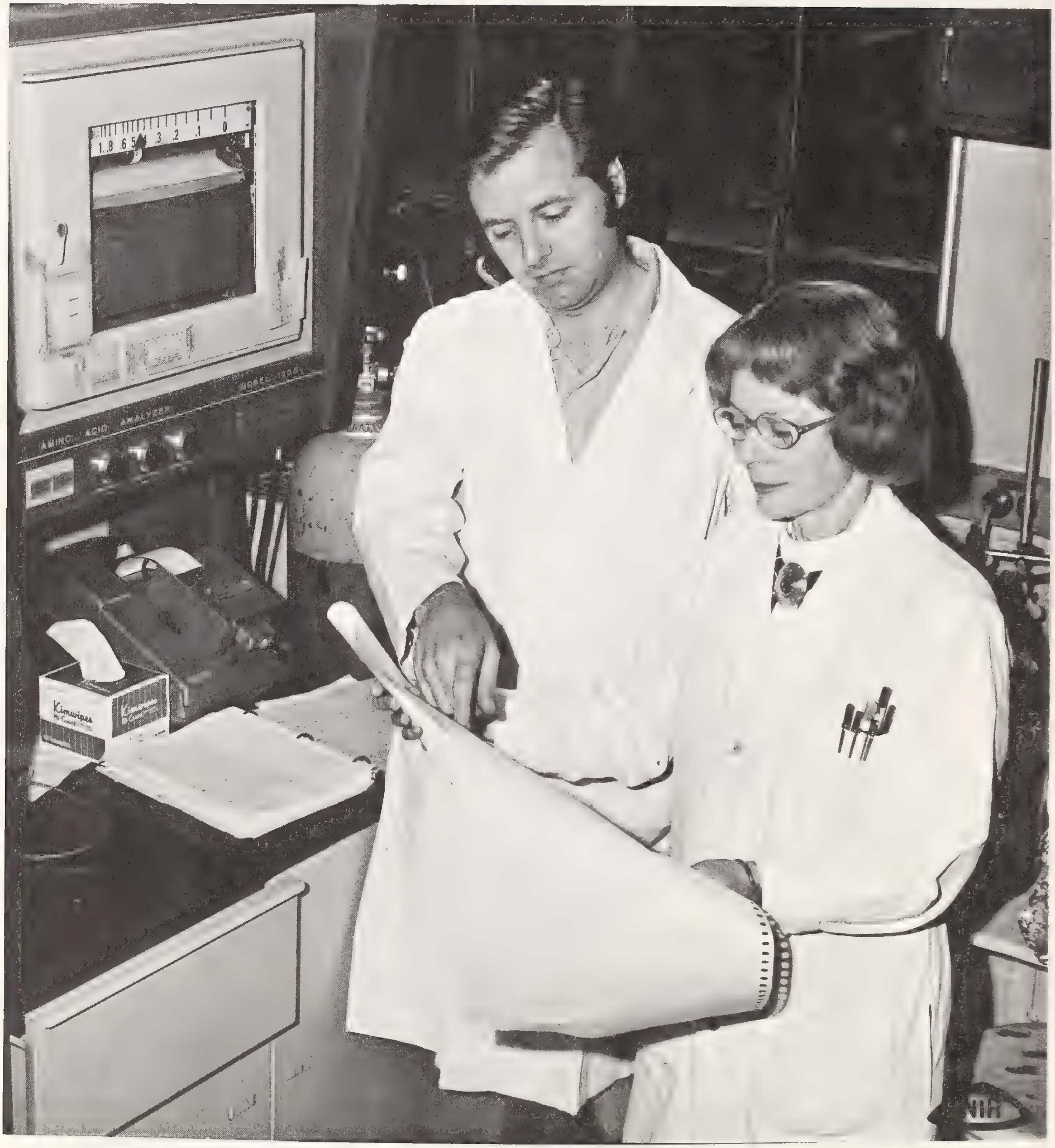
GAINESVILLE, FL--Dr. James E. McGuigan is studying the relationship of certain gastrointestinal hormones to digestive diseases in his laboratory at the University of Florida J. Hillis Miller Health Center. The National Institute of Arthritis, Metabolism, and Digestive Diseases administers the NIH funded research program into the problem of digestive diseases. (NIH Photo #D-11)



IOWA CITY, IA--Discussing procedures necessary for the study of the contractions of isolated colon muscle is Dr. James Christensen (right), professor of internal medicine at the University of Iowa-VA Hospitals, with Jan Miller, medical technologist. Five years ago, Dr. Christensen discovered the electrical slow wave of the colon which appears to function as a "pacemaker" for the rhythmic contractions of the colon. Dr. Christensen is also studying the physiological characteristics which define the lower esophageal sphincter and its role in reflux esophatitis. Funds for research into digestive diseases are administered by the National Institute of Arthritis, Metabolism, and Digestive Diseases. (NIH Photo #D-12)

LA JOLLA, CA--Dr. Henry O. Wheeler, professor of medicine at the University of California, San Diego School of Medicine, monitors the atomic absorption spectrometer to measure calcium, sodium, and potassium concentrations in bile and other body fluids. Support for digestive diseases research is administered by the National Institute of Arthritis, Metabolism, and Digestive Diseases. (NIH Photo #D-13)

LOS ANGELES, CA--The diagnosis and treatment of peptic ulcers are of special interest to Morton I. Grossman, M.D., of the University of California, Los Angeles. In the UCLA Department of Physiology he is studying digestive diseases under a grant from the National Institute of Arthritis, Metabolism, and Digestive Diseases. (NIH Photo #D-14)



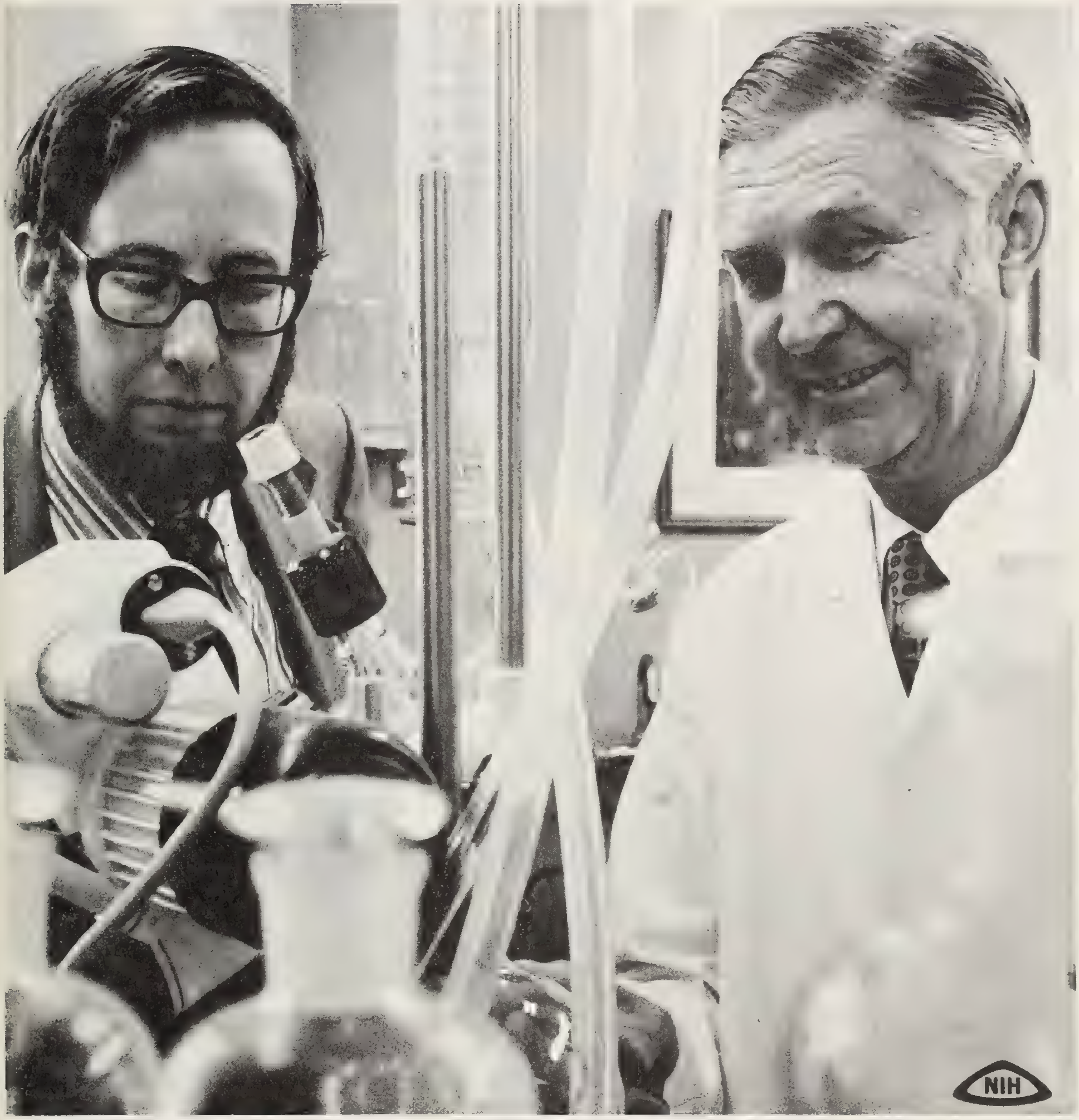
MILWAUKEE, WI--Studies on the structure and activity of bovine pepsin at the Medical College of Wisconsin are headed by Beatrice Kassell, Ph.D., professor of biochemistry. Dr. Kassell and Peter Ward, a graduate student, are shown reviewing data on an analysis of purified pepsin carried out in the amino acid analyser. An NIH component, the National Institute of Arthritis, Metabolism, and Digestive Diseases, administers research into the problem of digestive diseases. (NIH Photo #D-15)

*NEW YORK, NY--Intestinal transport mechanisms and basic physiology studies of the small intestine are being conducted by Dr. David Schachter of the Columbia-Presbyterian Medical Center. Research into the problem of digestive diseases is supported by the National Institute of **Arthritis**, Metabolism, and Digestive Diseases. (NIH Photo #D-16)*

NEW YORK, NY--Research on pancreatic and inflammatory bowel diseases is conducted at the Mount Sinai Medical Center by Dr. Henry D. Janowitz of the Department of Medicine. Dr. Janowitz (left) is shown with Dr. Charles Gerson. Administering the digestive diseases research program is the National Institute of Arthritis, Metabolism, and Digestive Diseases. (NIH Photo #D-17)

NEW YORK, NY--Dr. Hans Popper continues to study the morphology and ultrastructure of normal and diseased tissues to elucidate the underlying causes of liver disease in the Department of Pathology of the Mount Sinai Medical Center, although he also serves as Acting President of the Center and Acting Dean of the Mount Sinai School of Medicine. Digestive diseases research is funded by the National Institute of Arthritis, Metabolism, and Digestive Diseases. (NIH Photo #D-18)

PHILADELPHIA, PA--Neurophysiological studies related to gastric ulcer disease are part of the research carried out by Frank P. Brooks, M.D., at the hospital of the University of Pennsylvania. His work is supported by NIH's National Institute of Arthritis, Metabolism, and Digestive Diseases. (NIH Photo #D-19)



ROCHESTER, MN--Studying the problem of digestive diseases are Dr. Charles Code and Dr. Alan Hofmann of the Mayo Clinic. Dr. Code is in the Department of Physiology and is studying the electrophysiology of the small intestines. Dr. Hofmann, who is in the Gastroenterology Unit, is doing research on biliary tract disease and gallstone formation. Funds for research into digestive diseases are administered by the National Institute of Arthritis, Metabolism, and Digestive Diseases. (NIH Photo #D-20)

SAN FRANCISCO, CA--At the University of California, San Francisco, Rudi Schmid, M.D., Ph.D. (left), and Antony McDonagh, Ph.D., are engaged in research on bilirubin metabolism and liver function. Dr. Schmid's research into the problem of digestive diseases is funded by NIH's National Institute of Arthritis, Metabolism, and Digestive Diseases. (NIH Photo #D-21)

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ST. LOUIS, MO--In the Department of Pathology at Washington University, Dr. Marie H. Greider is working on the relationship of the hormone, gastrin, to peptic ulcer disease. Support for digestive diseases research is administered by the National Institute of Arthritis, Metabolism, and Digestive Diseases. (NIH Photo #D-22)

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March 10, 1973

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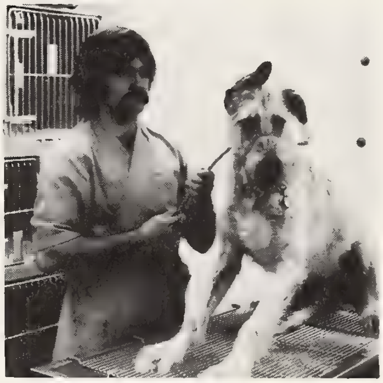
NIH Portfolio on Population Research



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Research Advances

In Rhesus Monkeys...

LOW-FAT, LOW-CHOLESTEROL DIET CAN REVERSE ATHEROSCLEROSIS

Atherosclerosis can be reversed in monkeys. National Heart and Lung Institute (NHLI) grantees at the University of Chicago report that a low-fat, low-cholesterol diet exerts a positive effect on the reversal of advanced experimental atherosclerosis in Rhesus monkeys. Additionally, the diet decreases the frequency and severity of the fatty deposits in the artery walls.

Since monkeys are commonly used as substitutes for humans in atherosclerosis research, the Chicago investigators suggest that these findings might apply to humans.

According to Draga Vesselinovitch, D.V.M., Research Associate (Assistant Professor) in the Department of Pathology at the University's Division of The Biological Sciences and The Pritzker School of Medicine, "The important question as to whether the atherosclerotic plaque can be reversed has received relatively little study in man or experimental animals. Most previous workers have considered this to be an irreversible disease, especially when it becomes severe."

Dr. Vesselinovitch explains that her studies at the University of Chicago, plus earlier studies at the University of Iowa by Mark Armstrong, M.D., and William Connor, M.D., have provided evidence that "at least to some degree even advanced stages of the disease can be reversed if low serum cholesterol levels are sustained for a long period of time."

(more)

During the first 18 months of the Chicago project, four groups of Rhesus monkeys (17 monkeys) received a diet containing 2 percent cholesterol, 12.5 percent coconut oil, and 12.5 percent butter fat. All four groups of monkeys had very high serum cholesterol levels at 18 months.

When the investigators autopsied Group I (five monkeys) at 18 months, they found severe atherosclerosis in the animals' aortas. (The aorta, leading directly out of the heart, is the principal artery carrying blood to the rest of the body in all mammals.) These aortic fatty deposits involved 81 percent of the surface area. Microscopic study of standard sections of the aorta revealed 70 percent incidence and a 37 percent severity rating.

In the succeeding 18 months, Groups II and III monkeys (five monkeys each) were fed low-fat, low-cholesterol diets of monkey chow supplemented with 5 percent corn oil. Additionally, Group IV (two monkeys) were continued on the high-fat, high-cholesterol diet given to all the monkeys in the first 18 months.

The investigators found that Group IV maintained almost the same high serum cholesterol level for the entire 36 months. Microscopic study of Group IV revealed 95 percent gross aortic lesions, 80 percent frequency, and 51 percent severity.

However, when they examined Groups II and III, the investigators found that the serum cholesterol levels had declined to quite low levels of 122 and 148 milligrams percent respectively by 36 months. These two low-fat, low-cholesterol groups had 46 and 31 percent of the surface areas of their

(more)

aortas covered by lesions when examined grossly. Microscopic study showed 56 and 47 percent frequency ratings and 19 and 14 percent severity ratings, respectively.

(These microscopic frequency ratings were based on the study of three sections each from the aorta of each animal and two additional sections from large branches of the aorta. The severity ratings employed a scale commonly used by pathologists based on different degrees and types of fatty deposits.)

Dr. Vesselinovitch reported the results of her study at the meeting of the American Association of Pathologists and Bacteriologists, Washington, D.C., February 25, 1973. This research was directed by Robert W. Wissler, M.D., Ph.D., the Donald N. Pritzker Professor in the Department of Pathology and the College and Director of the University's Specialized Center of Research on Atherosclerosis (SCOR). The SCOR is supported by grants from NHLI.

NOTE TO SCIENCE WRITERS: For additional information about Dr. Wissler's studies of diet and atherosclerosis, see NEWS & FEATURES From NIH, *November 25, 1972, "Monkeys Fed Average American Diet Suffer Heart and Artery Damage."*

#

Research Advances

CHIMPS MAKE TOOLS, PRACTICE DENTISTRY

Chimpanzees at the Delta Regional Primate Research Center inspect, clean, and extract their own and each other's teeth. In their practice of "dentistry," the animals make and use stick tools to supplement the use of their fingers. This represents the first example of repeated tool use by animals in social grooming.

Three male and four female chimpanzees have lived as a group in a one-acre outdoor enclosure at the Primate Center for three-and-one-half years. All were born in the wild and are now adolescents and young adults aged seven to 11 years old.

The chimpanzees live in an enclosure which includes natural herbaceous vegetation and contains upright and fallen posts or tree trunks and movable objects. Additionally, fresh woody branches and saplings are introduced regularly for the animals' use. The chimps are allowed to lead as self-regulating and naturalistic a life style as possible.

The NIH Division of Research Resources provides support for these facilities at the Delta Regional Primate Research Center, Tulane University.

The activities of this group of animals were observed from an over-deck with binoculars and a camera with a telephoto lens. In 135 hours of observation, 45 bouts of dental grooming and 4 uses of tools were noted.

Observers first recorded dental grooming among the chimpanzees when Belle, an 8-year-old female chimp, used a 6-inch twig to groom the teeth of Bandit, a 7-year-old male. Four types of dental grooming could then be

(more)

distinguished, with Belle acting as "dentist" and Bandit as her favorite "patient" in the first three types:

Social dental grooming involving tools
Social dental grooming not involving tools
Unsuccessful attempts at social dental grooming
Self-dental-grooming

Belle's usual procedure began with normal social grooming directed to the hair of Bandit's limbs, torso, or head. Then, she concentrated on his face and finally opened his mouth. If Bandit cooperated by gaping his jaws, Belle began dental grooming with her fingers, using the two forefingers as forceps to remove a particle. She spontaneously picked up sticks from the surrounding area as supplementary aids. Her usual practice was to steady the patient's head with one hand while working with the other.

Belle sometimes held the tool between her lips like a cigarette and alternated bouts of dental grooming with the fingers and with the tool. In some instances, she modified the sticks by stripping off leaves, breaking off pieces, or chewing off ends.

These bouts of dental grooming, lasting from three to 15 minutes, were probably instigated by Bandit's shedding of deciduous molars.

The observers recorded a significant instance of Belle's extraction of one of Bandit's teeth. She began working on Bandit's lower left second premolar, using a cigarette-sized pine twig. Bandit lay supine and Belle sat close beside his head. After a minute and a half of manipulations, the tooth was dislodged.

(more)

The observers recorded the use of tools in self-grooming a few months later. They witnessed Shadow, a 9-year-old male chimpanzee, using a 10-inch tine from a discarded rake to scrape at his upper molars for 30 seconds. (The rake had been inadvertently left in the enclosure and the animals had dismantled it in play.)

In the following weeks, tool use in self-dental-grooming became more complex. Using a variety of stick tools, Belle continuously probed and picked at her lower left premolars for almost 30 minutes. In one instance, she modified the same tool several times by breaking off the ends as they wore down. Shadow also practiced self-dental-grooming, but he picked at his tooth with his thumbs, rather than with a tool.

The observers witnessed self-extraction of a deciduous tooth by Bandit. To remove his lower left first premolar, the chimpanzee used the principle of dental floss, another innovation in tool use in the group. He used a ribbon-like piece of cotton cloth that was knotted in the middle and 21 inches long and one-half inch wide. (It was a scrap remaining from articles of old clothing thrown in for the animal's play activities.)

With one end in each hand, Bandit pulled the taut cloth strip from side to side across the mandibular gingiva and against the loose tooth. He also pulled the cloth backward and forward, perpendicular to the line of the teeth in the gingiva. The observers speculate that one of these jerks dislodged the tooth.

Bido, an 8-year-old female chimp, extracted an upper right deciduous canine tooth. In a session lasting slightly more than 20 minutes, she used

(more)

two tools and her forefinger to extract the tooth.

Apart from its obvious hygienic function, this dental grooming reinforces bonds between the animals through prolonged intimate interaction and mutual aid. However, the particular cause for these instances of dental grooming remain unclear and no single explanation can be found for the rise and continued development of this unique custom in the group of chimpanzees. The observers strongly suspect that the grooming was connected to the loss of deciduous teeth and made possible by the animals' extensive experience with object manipulation.

Under specific laboratory or zoo conditions, many primates are capable of complicated tool use, often with help from human intervention. However, this spontaneous use of tools was shown by animals living in a self-regulating, natural life. No human reinforcement was given.

William C. McGrew, Ph.D., and Caroline E.G. Tutin of the Stanford University Department of Psychiatry published reports of their observations in the *Journal of the American Dental Association*, December 1972, and in *Nature*, February 16, 1973.

#

Research Advances

ATYPICAL MEASLES SEEN IN SOME CHILDREN IMMUNIZED WITH ATTENUATED VACCINES

"Atypical measles," an unusually severe and aberrant form of the disease, has been found in some children who were immunized previously with attenuated live measles virus vaccines as much as seven years prior to onset of their illness. The discovery was made by physicians in St. Louis, Missouri, supported in part by the National Institute of Allergy and Infectious Diseases (NIAID).

Prior to the discovery by the St. Louis doctors, atypical measles was thought to be a problem only in children immunized previously with killed or inactivated measles vaccines. These vaccines are no longer used in the United States.

The new cases of atypical measles were seen during the winter and spring of 1970 to 1971, when an epidemic occurred in the St. Louis area. During a multifaceted study of this epidemic, funded in part by NIAID, doctors performed clinical and blood studies on 140 children suspected of being measles vaccine failures. In this group, 12 children had clinical illnesses suggestive of the atypical measles syndrome. Six of these children had received the killed vaccines, but six had received only the live attenuated vaccines. The symptoms of the two groups were quite similar, although the illness was more severe in recipients of the killed vaccines.

Since physicians no longer use inactivated measles vaccines, atypical measles resulting from their previous use is not expected to be a continuing

(more)

problem. The findings of this present study suggest, however, that similar aberrant reactions may also occur in recipients of attenuated measles vaccines. The investigators caution that with increasing time periods from measles immunization to the time of natural measles exposure, more frequent and perhaps bizarre reactions could occur.

This study was reported in the November 1972 issue of *Pediatrics* by James D. Cherry, M.D., Ralph D. Feigin, M.D., Louis A. Lobes, Jr., M.D., and Penelope G. Shackelford, M.D.

#

Photo Feature

SLE Treatment...

SCIENTISTS GIVE ANIMALS NEW TRIPLE-DRUG THERAPY

A new study of triple-drug therapy for systemic lupus erythematosus (SLE), an inflammatory disease of connective tissue, is being initiated on the basis of animal investigations at the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) and at Walter Reed Army Medical Center.

The scientists report that simultaneous administration of three potent drugs effectively retards the disease process in NZB/W mice, a strain of rodents which develops an SLE-like disorder spontaneously as they grow older. Beneficial effects were attained without increased drug toxicity by use of low doses of each drug, and it is believed that evaluation of similar treatment in human SLE patients may be warranted.

SLE is one of a family of diseases, such as rheumatoid arthritis and rheumatic fever, in which the body's connective tissue is affected abnormally. It may begin with any number and combination of symptoms and, subsequently, produces alterations in the structure and function of the skin, joints, and internal organs, particularly the kidneys. SLE frequently affects young women between the ages of 15 and 40, and there is no completely satisfactory form of therapy.

Dr. Alfred D. Steinberg of the NIAMDD, and his colleagues at Walter Reed, aimed their treatment specifically at the nephritis which occurs in many SLE patients and which may be fatal. Mice receiving all three drugs--

(more)

azathioprine, cyclophosphamide, and methylprednisolone--had significantly less protein in the urine, lower anti-DNA antibody activity, less microscopically evident kidney disease, and greater survival rates than mice treated with one or two of these drugs.

Survival rates after one year of treatment were 44 percent in mice receiving one drug, 37 percent in those receiving two drugs, and 86 percent in those receiving three drugs. The data obtained in this study suggest that the three drugs employed can act in unison with regard to both their immunosuppressive and anti-inflammatory properties. Similar combined immunosuppressive drug regimens have been utilized recently in the treatment of malignancies, allograft rejection, and immunologically mediated diseases.

Because the hereditary SLE-like syndrome of NZB/W mice is an excellent model for human SLE, these studies may provide the experimental rationale for undertaking controlled clinical trials of combination immunosuppressive drug therapy in human SLE nephritis.

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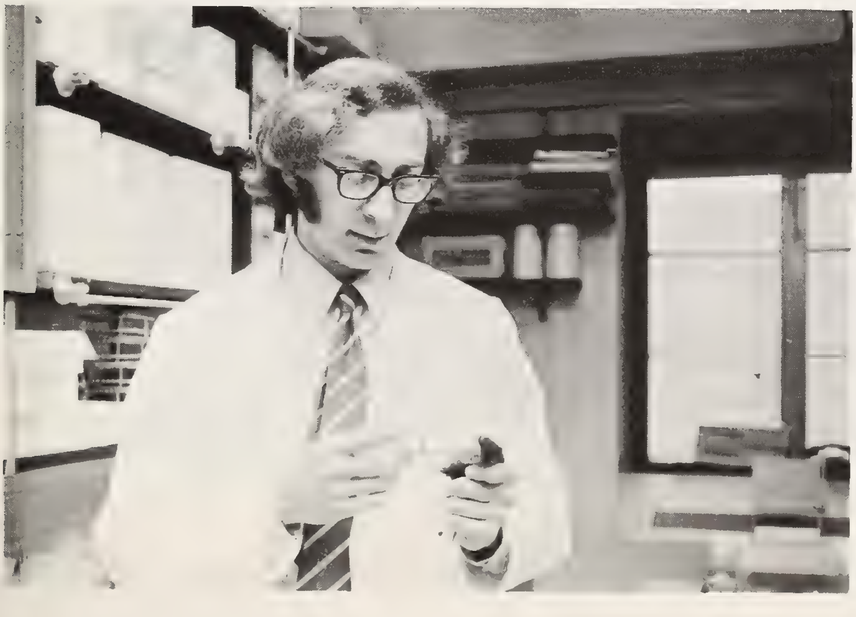

Dr. Steinberg is injecting a mouse with one of the three drugs he is using in a new study of therapy for systemic lupus erythematosus. Only animal trials have been conducted so far. He is a Senior Investigator in the NIAMDD Arthritis and Rheumatism Branch. (NIH Photo #1010)

SLE (Cont'd)

Alfred D. Steinberg, M.D., of the National Institute of Arthritis, Metabolism, and Digestive Diseases, is studying a new triple-drug therapy for systemic lupus erythematosus. Dr. Steinberg and biologist Susan Kysela are shown (above) injecting a mouse with one of the drugs. In the lower photo, Michael C. Gelfand, M.D. (left), is diluting a drug before Dr. Steinberg injects it into a mouse. Dr. Gelfand is a Special Fellow in the Laboratory of Immunology of the National Institute of Allergy and Infectious Diseases. He was formerly a Staff Physician at Walter Reed Army Medical Center. (NIH Photo #1011 and 1012)

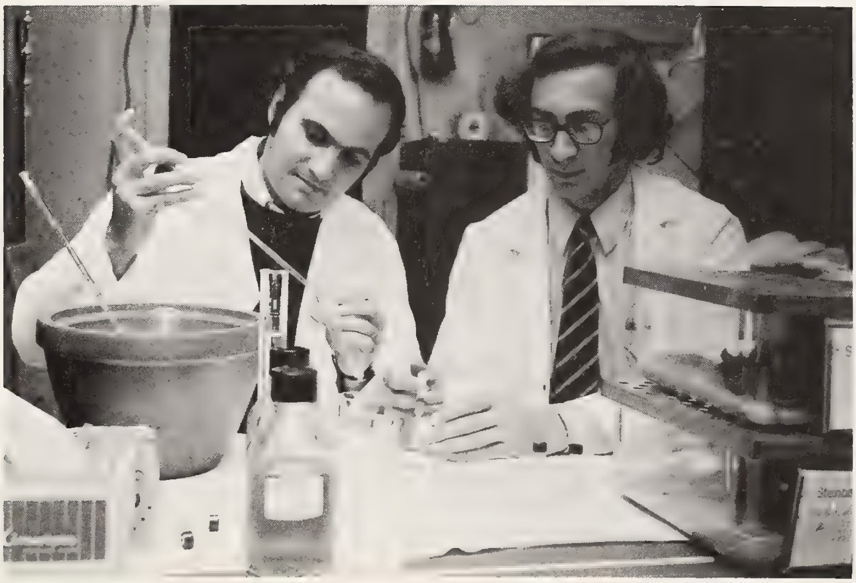

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Photo Feature

NIH Grantees...

UNIVERSITY OF WASHINGTON SCIENTISTS PURSUE VARIED MEDICAL PROBLEMS

At the University of Washington Health Sciences Center, Seattle, Kate L. Kogan, Ph.D. (above), Professor of Psychiatry, instructs a mother who is playing with her child. Dr. Kogan is separated from the mother and her child by a one-way mirror. The mother listens through an earphone for suggestions on ways of responding to her child. Through Dr. Kogan's research, which is supported by the National Institute of Neurological Diseases and Stroke (NINDS), she teaches mothers of children with emotional or motor difficulties more effective ways of dealing with their children. She also makes these methods available to others who work with mothers and their children. Another NINDS grantee, Patricia W. Hayden, M.D. (upper right), Assistant Professor, Pediatrics, studies the effects of drugs on a hydrocephalic dog in order to find improved treatment of hydrocephalic children. Ingegerd E. Hellstrom, M.D, Ph.D. (lower right), Professor of Microbiology, performs microcytotoxic tests on human tumors. Dr. Hellstrom's studies of the immune response in human and animal tumor systems are supported by the National Cancer Institute. (NIH Photos #1013, 1014, 1015)

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Photo Feature

14,000 Aided...

OPERATION MEDIHC HELPS VETERANS FIND PLACES IN CIVILIAN HEALTH

More than 14,000 veterans with health skills and knowledge have been referred to occupational and educational opportunities in the health field through Operation MEDIHC.

MEDIHC (Military Experience Directed Into Health Careers) is a counseling and referral program administered by the individual states under contract with the Bureau of Health Manpower Education's Division of Allied Health Manpower, and in cooperation with the Department of Defense.

Of the 14,000 people assisted since 1970, about 60 percent are in various health field jobs, and the rest are in educational programs that will expand their military service health training.

MEDIHC agencies located throughout the nation give referral service, educational counseling, and other specialized services to former medics who wish to have a meaningful role in civilian health professions.

Servicemen and women are eligible for MEDIHC services 90 days prior to their separation date. Transition officers at separation bases have MEDIHC application forms which when completed are sent to the MEDIHC agency in the state where the applicant wants to locate after discharge. The state MEDIHC coordinator provides the applicant with information about available job and training opportunities which seem to be compatible with employment needs, previous training and experience, and career plans. Information about the applicant is provided by the MEDIHC coordinator to potential employers.

(more)

Results and future plans for Operation MEDIHC will be discussed at the National MEDIHC Conference, March 21 to 23 in Washington, D.C.

Operation MEDIHC referred Dale Lambeth (1) who became head of the St. Joseph (MO) Hospital's Unit Manager Program; James J. Melstrom (2) who has animal care responsibilities at Gehrman Animal Hospital, Minneapolis; Larry W. Alderton (3) who serves as a burn technician at Shriners Hospital for Crippled Children, Boston; and James E. Farrow (4) who is a registered medical technologist at Audrain Medical Center, Mexico (MO).

(more)

MEDIHC (Cont'd)

William Brown (above right) is an emergency room medical specialist at Washington DC's George Washington University Hospital. A former medic, he was referred to the hospital through Operation MEDIHC. This program is part of the National Institutes of Health's Bureau of Health Manpower Education. Referred through the same program was Arcadio Gonzalez (below left), manager of Norwalk (CT) Hospital's Department of Respiratory Technology.

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Medical News Tip

SOVIET AND AMERICAN RESEARCHERS FIGHT HEART DISEASE--Soviet and American heart experts are cooperating on a research attack against the greatest cause of death in both countries--coronary heart disease. The aim of the project, officially titled the "Cooperative Project on Management of Ischemic Heart Disease," is to evaluate and compare chronic angina and heart attack disability treatment methods that have been developed separately in each country.

Ischemic heart disease occurs when the blood vessels to the heart muscle (coronary arteries) are narrowed by arteriosclerosis.

Some of the most popular methods in the U.S. for treating chronic disability from heart attacks and angina--such as coronary artery surgery--are virtually untried in the U.S.S.R. patient population. Conversely, some of the most elaborate and interesting medical approaches in the U.S.S.R. are unfamiliar or unknown to U.S. heart specialists.

This project is one of several which are concerned with different heart problems. All are components of the broad "U.S.-U.S.S.R. Cooperative Health Program on Disease" launched by the governments of both nations last year.

For information about these cooperative projects, contact: National Heart and Lung Institute Information Office, Landow Building, Room C-918, Bethesda, MD 20014, Phone: (301) 496-4236.

#

New Publication:
Dental Replants, Transplants, and Implants

In *Dental Replants, Transplants, and Implants,* a new brochure from the National Institute of Dental Research (NIDR), the Institute offers some facts about these three areas of dental research.

Replants are teeth that have been knocked out by accident and then replaced in the same socket. According to the brochure, the replant procedure is relatively simple, often painless, and works most effectively on a child's tooth which has been out of the mouth less than an hour.

Dental transplants are natural tissues or organs which are inserted as a replacement for a missing tissue or organ, coming from the same person or from someone else. NIDR studies have shown that soaking the tooth in a fluoride solution may prolong the success of the transplanted tooth. The researchers are presently studying methods of transplanting teeth between siblings with closely matched tissues in an effort to slow rejection and prolong tooth survival.

Dental implants are non-living materials placed in the body to substitute for damaged or missing parts. For the past 20 years, researchers have investigated surgical metals, plastic covered metals, acrylic plastics, and ceramics as dental implants. However, NIDR does not recommend any type of tooth implant for public use.

Science writers and editors may obtain a copy of this publication from: NIDR Information Office, Bldg. 30, Room 126, NIH, Bethesda, MD 20014, Phone: (301) 496-4261.

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News Releases Issued

IMMUNOTHERAPY REGISTRY--An International Tumor Immunotherapy Registry has been established by the National Cancer Institute to serve as a center for collection, storage, and exchange of information on immunological methods of treating cancer. The Registry will record physicians' experience with immunotherapy for human cancer, including methods of administration, results of the treatment, and possible side effects. It will be kept up to date by periodic progress reports from the physicians, who will in turn receive newsletters containing summaries of the most recent information. Computers are expected to handle much of the work involved. The Registry will be a service of the International Cancer Research Data Bank, which is currently being organized as a result of the National Cancer Act of 1971.

#

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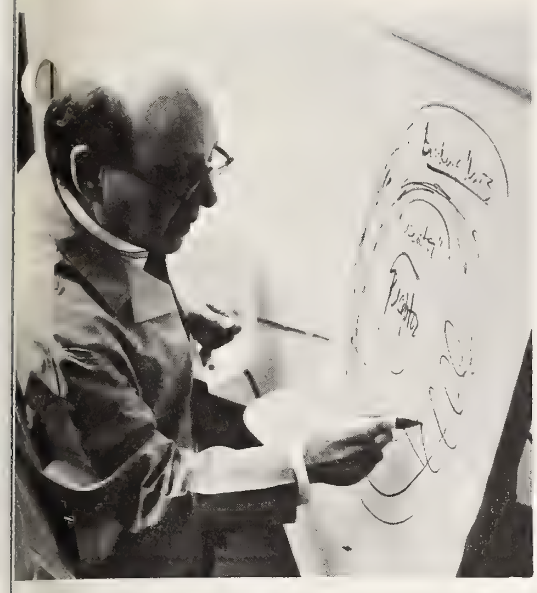
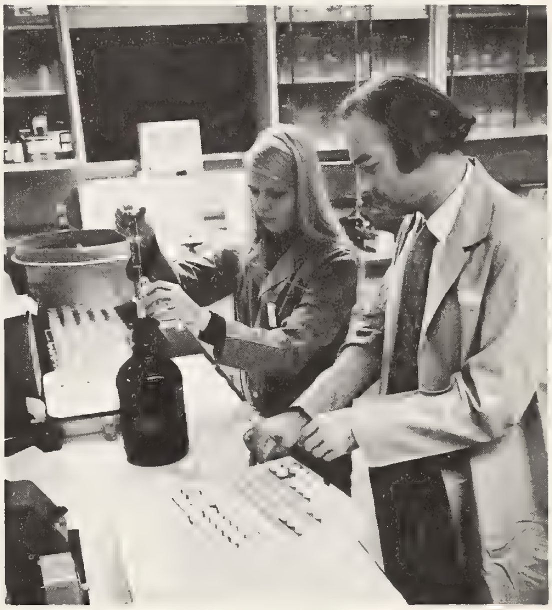
POPULATION RESEARCH





NEWS&FEATURES FROM NIH

NIH PORTFOLIO ON POPULATION RESEARCH....MARCH 1973

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE ■ Public Health Service ■ National Institutes of Health ■ Office of Information ■ Bethesda, Maryland 20014

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INTRODUCTION: NICHD CENTER FOR POPULATION RESEARCH PROBES BIOMEDICAL AND SOCIAL PROBLEMS

This Introduction was prepared by Philip A. Corfman, M.D. (left), and William A. Sadler, Ph.D. of NIH's National Institute of Child Health and Human Development. Dr. Corfman is Director of the Center for Population Research, while Dr. Sadler is Acting Chief of the Population and Reproduction Grants Branch.

Major programs in population research are presently being conducted at seven Population Research Centers and eight Program Projects supported by the Population and Reproduction Grants Branch, Center for Population Research, National Institute of Child Health and Human Development (NICHD). These Centers and Program Projects focus on biomedical as well as behavioral-social aspects of population research and represent extensions of the Federal Government's participation in the search for solutions to population problems.

POPULATION RESEARCH CENTERS

On July 1, 1970, the Center for Population Research of NICHD announced a new program to provide funds for core support and program development for non-profit organizations in the United States conducting research and training relevant to population problems.

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Center awards are used directly to furnish salaries of personnel, supplies, laboratory equipment, travel and publication costs, and to institute new research programs that will contribute to outstanding multi-disciplinary research in population problems. So far, seven centers in the United States have been funded. They are located at Johns Hopkins University, the Population Council, The University of Texas at Austin, the University of Wisconsin, Harvard University, the University of Chicago, and Vanderbilt University.

The Population Research Center at Vanderbilt University was directed until recently by Bert W. O'Malley, M.D. He was Professor and Occupant of the Vanderbilt Chair of Reproductive Biology and Family Planning. Dr. O'Malley has moved to a position at the Baylor College of Medicine, Houston. The acting director of the Center at Vanderbilt is now Marie-Claire Orgebin-Crist, Ph.D.

PROGRAM PROJECTS

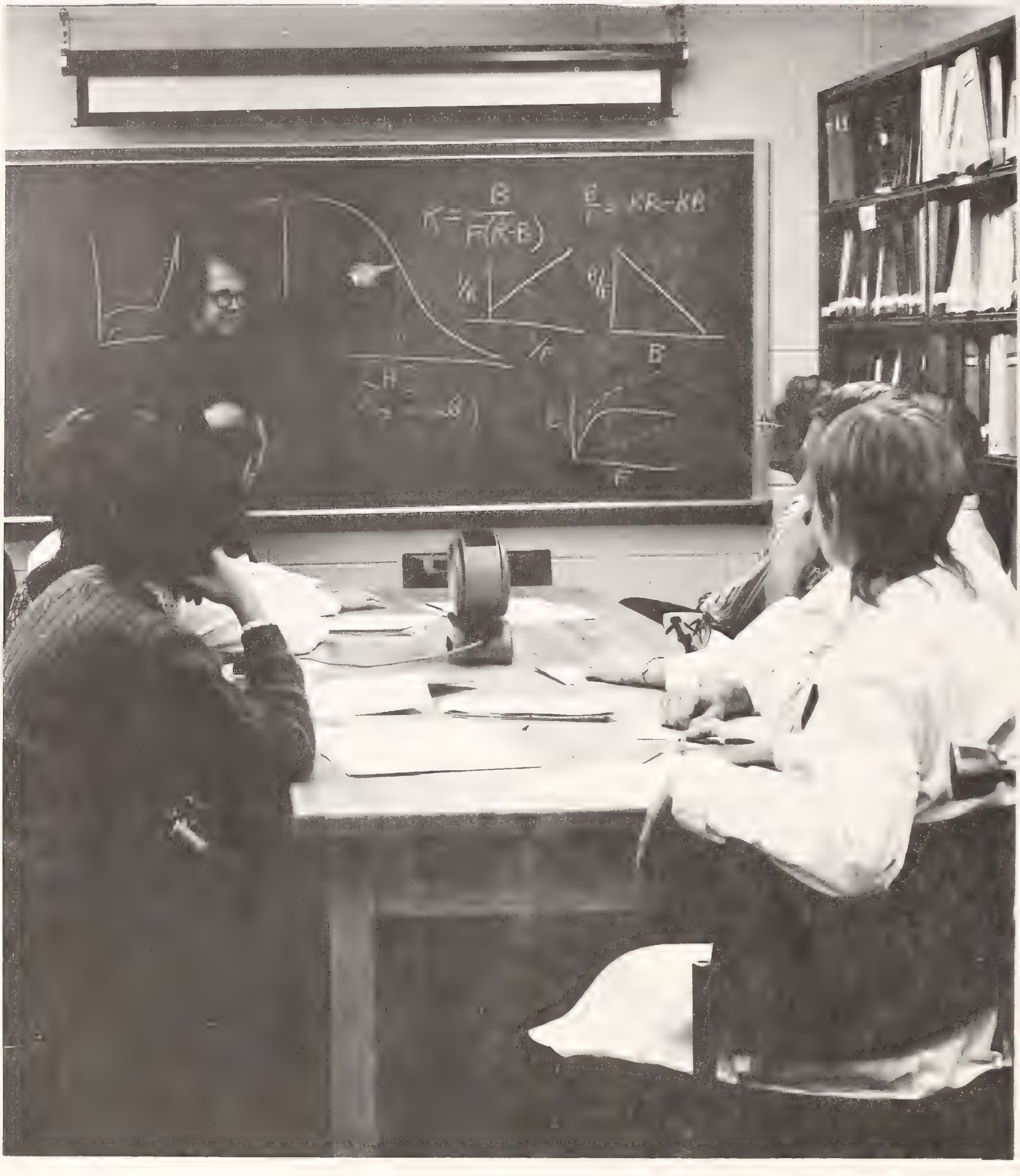
A second large program administered by the Population and Reproduction Grants Branch, CPR, NICHD, provides support for program projects in population research. Program project grants provide for the direct support of inter- or multi-disciplinary population research and serve to coordinate many research activities for the purpose of achieving a common set of well-defined goals. Unlike the project grant, the program project is designed to facilitate the pooling of ideas and skills required for the solution of complex problems in population research by encouraging the cooperation of many talented investigators and providing the core facilities for them to share in their work.

Some of the specific areas of reproductive biology which are currently being supported by Program Project grants include the physiologic, biochemical, and biosynthetic mechanisms involved in regulation of the menstrual cycle, the physiology and transport of sperm, fertilization and mechanism of implantation, physiology of conception, and the assay and role of hormones in early pregnancy.

Eight such Program Projects are currently being supported in the United States at Columbia University, University of Hawaii, the University of Michigan, Northwestern University, Ohio State University, Oregon Primate Research Center, University of Pennsylvania, and the University of Texas at Austin.

As a result of the management and large-scale funding of these unique approaches to population research, the Population and Reproduction Grants Branch, CPR, NICHD has made major contributions toward the advancement of knowledge in population research as well as the development of new and significant possibilities for fertility regulation and the alleviation of infertility.

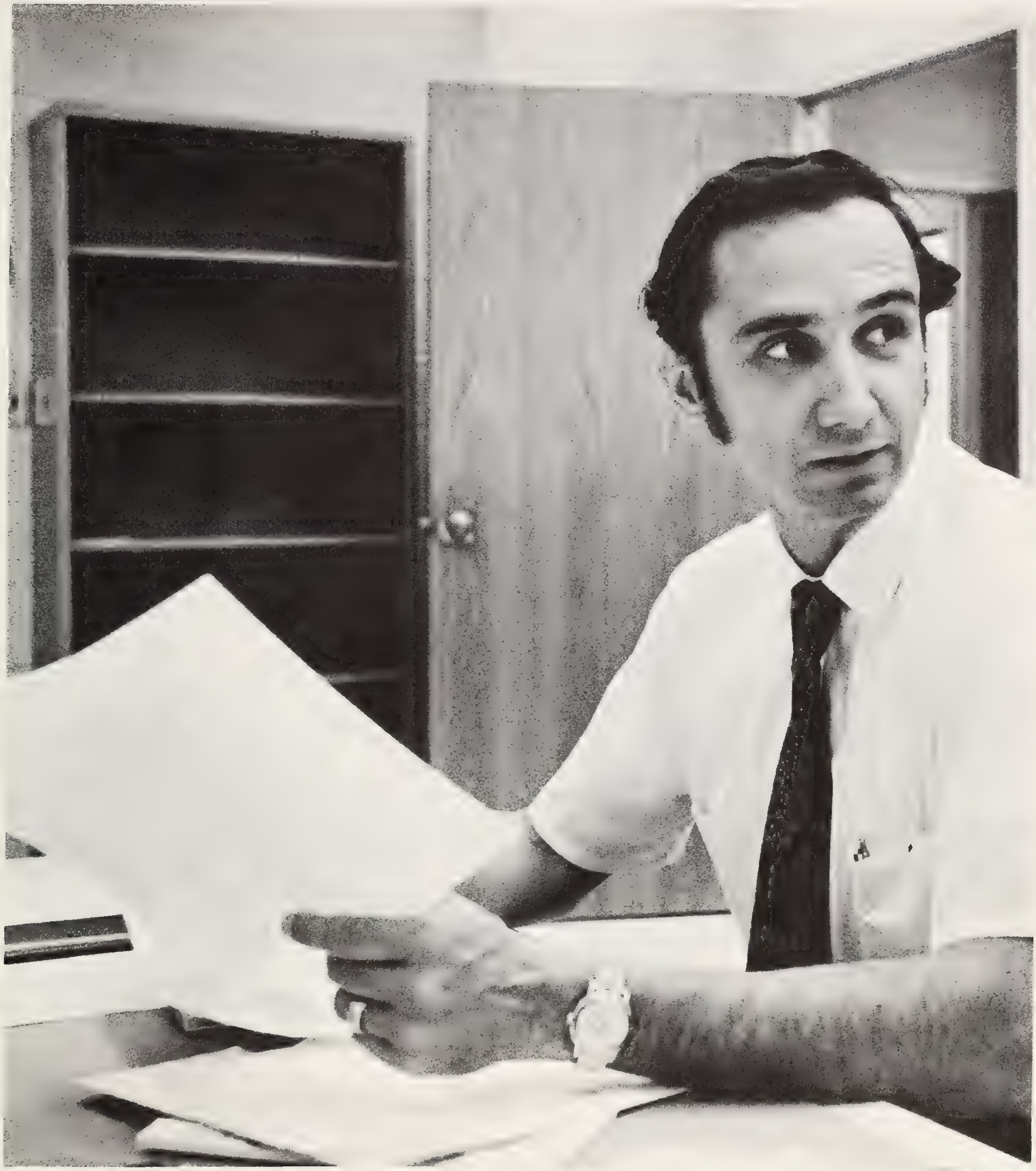
The National Institute of Child Health and Human Development is a component of the National Institutes of Health, an agency of the U. S. Department of Health, Education, and Welfare. NIH headquarters are in Bethesda, Maryland.



ANN ARBOR, MI--Dr. A. Rees Midgley (standing), principal investigator of the Population Research Program Project at the University of Michigan Medical School, discusses findings with his staff. NIH funds the project through the Center for Population Research of the National Institute of Child Health and Human Development. (NIH Photo #P-1)

AUSTIN, TX--Using a detailed tract map of San Antonio, Dr. Harley L. Browning (left), Director of the Population Research Center at the University of Texas, and Dr. Dudley L. Poston discuss factorial ecology, a statistical method of relating sub-areas within a city. Research at the Center is supported by a grant from the Center for Population Research of NIH's National Institute of Child Health and Human Development. (NIH Photo #P-2)

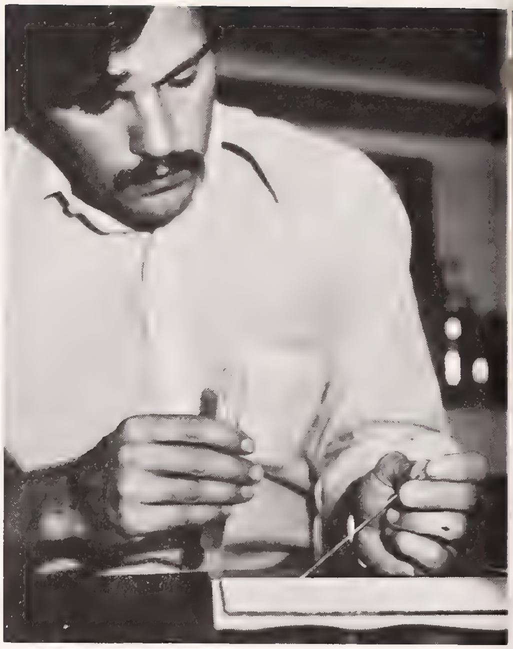
*AUSTIN, TX--Dr. Kenneth D. Lanclos prepares to inject a single dose of estradiol-17 B hormone into a male African Clawed Toad (*Xenopus*), as Dr. Terrell H. Hamilton (center) and Dr. Antone G. Jacobson watch. The investigation of the actions of various steroid hormones on the liver of the toad is part of the Population Research Program Project at the University of Texas, which is supported by the National Institute of Child Health and Human Development of the National Institutes of Health. Dr. Jacobson is principal investigator of the Project, which is administered by the Center for Population Research. (NIH Photo #P-3)*

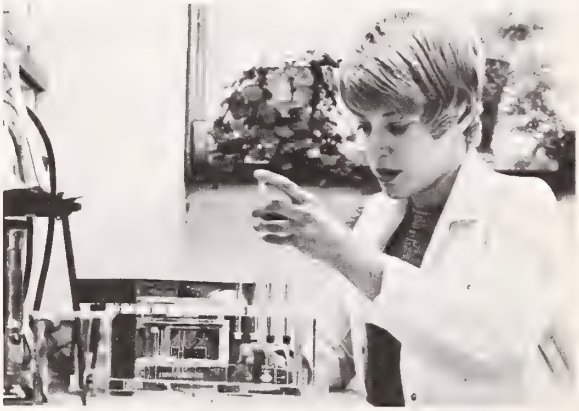


BALTIMORE, MD--W. Henry Mosley, M.D., documents the research activities of the Population Research Center at The Johns Hopkins School of Hygiene and Public Health. The National Institutes of Health supports the Center through grants administered by the Center for Population Research of the National Institute of Child Health and Human Development. (NIH Photo #P-4)

BEAVERTON, OR--Dr. Reed Norman (left) and Dr. Miles Novy of the Oregon Regional Primate Research Center use a small pediatric-size laparoscope to follow the ovulatory pattern of a rhesus monkey. The laparoscope permits the researchers to make internal observations with only a small puncture-type incision and with minimum sedation of the animal. By regulating the flow of CO_2 *gas through the laparoscope, the scientists can inflate the wall of the muscles enough to allow visual observations. The instrument also permits the taking of biopsies or visually following follicular changes on the ovary and ovulatory patterns without making a large incision. NIH's National Institute of Child Health and Human Development supports these investigations through a Population Research Program Project from the Center for Population Research. (NIH Photo #P-5)*

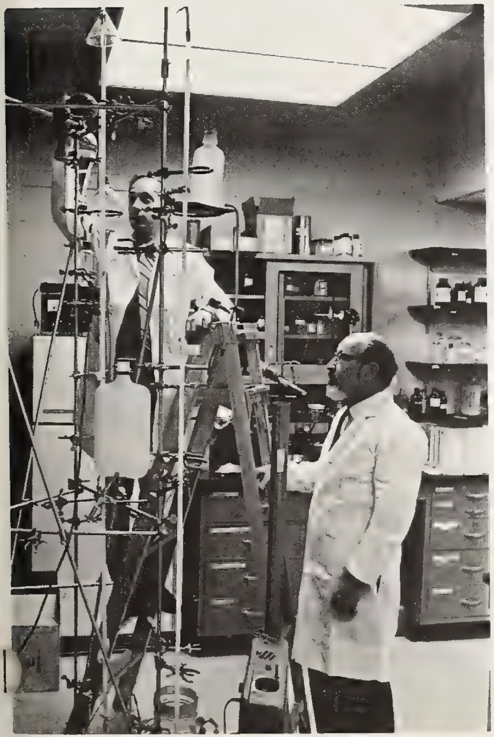
BOSTON, MA--Dr. Gordon Macdonald (left) and Dr. Lawrence Demers prepare a monkey for surgery in the Population Research Center at Harvard Medical School. Dr. Roy O. Greep is Director of the Center, which is supported by the Center for Population Research of NIH's National Institute of Child Health and Human Development. (NIH Photo #P-6)



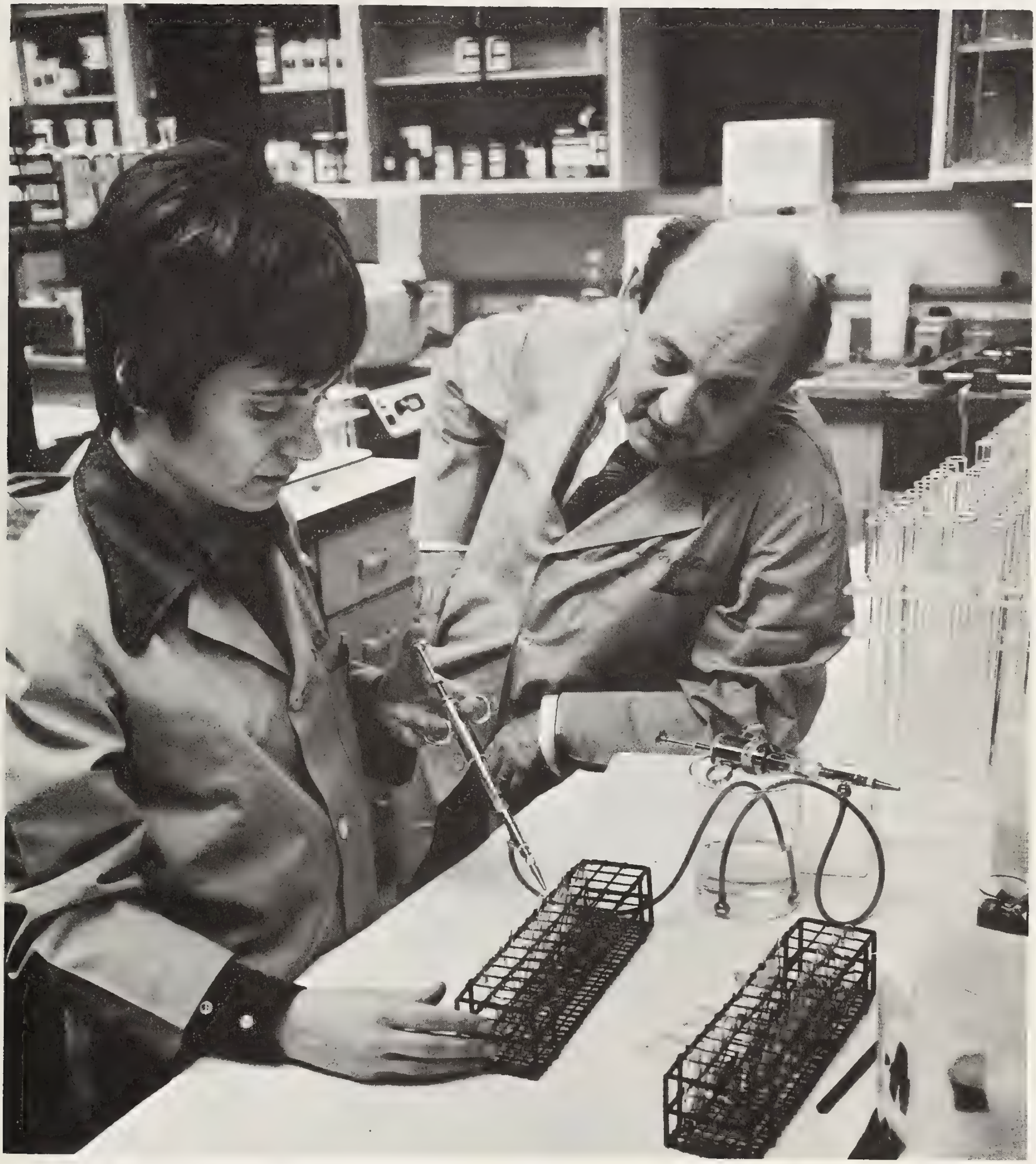


POPULATION RESEARCH CENTERS
AND
PROGRAM PROJECTS

NIH



CHICAGO, IL--Dr. Elwood V. Jensen is shown operating scintillation spectrometer as part of his research work. Dr. Jensen directs the University of Chicago Population Research Center, which is funded by the Center for Population Research of NIH's National Institute of Child Health and Human Development. (NIH Photo #P-7)



CHICAGO, IL--Dr. Oscar Hechter (right) observes as Dr. Mariel Birnbaumer measures the activity of enzymes activated by sex steroids in prostate nuclei. Dr. Hechter is the principal investigator at Northwestern University's Population Research Program Project, which is supported by the National Institute of Child Health and Human Development of the National Institutes of Health through its Center for Population Research. (NIH Photo #P-8)

COLUMBUS, OH--Dr. Noland L. Van Demark (right), Director of the Population Research Program Project at Ohio State University, and S. P. Singal check a radiochromatogram scanner to determine levels of hormones in rat testis tissue. Their research is funded by the Center for Population Research of NIH's National Institute of Child Health and Human Development. (NIH Photo #P-9)

HONOLULU, HI--Dr. Virgil Jacobs prepares the medulla oblongata of a human brain for observation at the University of Hawaii's Population Research Program Project. This research is supported by the Center for Population Research of NIH's National Institute of Child Health and Human Development. (NIH Photo #P-10)

MADISON, WI--Halliman H. Winsborough, Ph.D., and James A. Sweet, Ph.D., examine computer printout on scientific investigations at the Population Research Center at the University of Wisconsin. Dr. Winsborough is director of the Center, which is supported by the Center for Population Research of NIH's National Institute of Child Health and Human Development. (NIH Photo #P-11)

NEW YORK, NY--Dr. Kenneth A. Laurence (left) and Dr. Sheldon J. Segal, Director of the Population Council at The Rockefeller University, discuss current research. The Council is a Population Research Center funded by the Center for Population Research, NIH's National Institute of Child Health and Human Development. (NIH Photo #P-12)

NEW YORK, NY--Dr. Samuel M. Wishik (center) leads a small interdisciplinary group discussion on a research project, with (clockwise from left) specialists in Economic Geography (Julia M. Shimmel), Psychology (Bernard G. Pasquariella), Anthropology (Susan C. Scrimshaw), and Public Health Administration (Donald W. Helbig). Dr. Wishik is Director of the Division of Social and Administrative Sciences of the International Institute for the Study of Human Reproduction at Columbia University, which is a Population Research Program Project supported by the Center for Population Research of NIH's National Institute of Child Health and Human Development. (NIH Photo #P-13)

PHILADELPHIA, PA--Scientists at the Population Research Program Project at the University of Pennsylvania flush the ovary of a rhesus monkey. Luigi Mastroianni, Jr., M.D., is the principal investigator of the Program Project, which is supported by the National Institutes of Health through its National Institute of Child Health and Human Development's Center for Population Research. (NIH Photo #P-14)

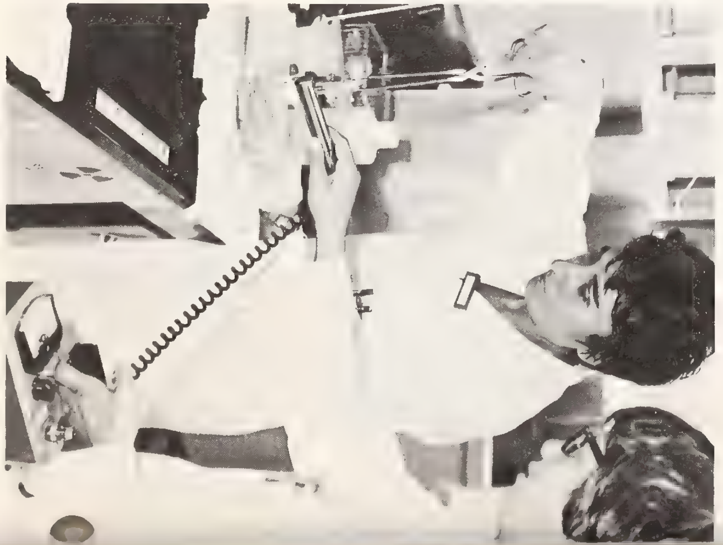
NEWS&FEATURES FROM NIH

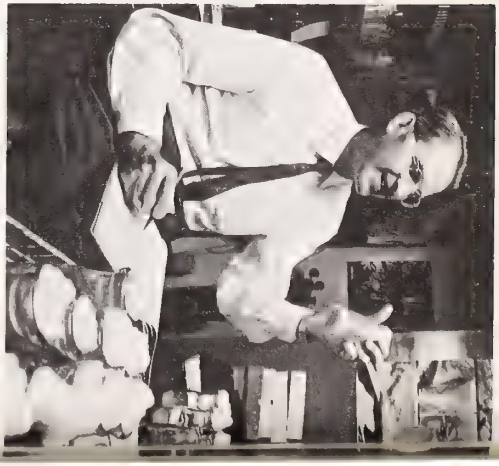
portfolio series

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE ■ Public Health Service ■ National Institutes of Health ■ Office of Information ■ Bethesda, Maryland 20014

POPULATION RESEARCH

march 1973





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March 25, 1973

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NEWS & FEATURES From NIH March 25, 1973

Research Advances

At Clinical Center...

BLOOD FROM VOLUNTARY DONORS REDUCES HEPATITIS INCIDENCE

Scientists at the NIH Clinical Center recently reported a fivefold decrease in hepatitis following surgery. Officials at the Center's Blood Bank say the decrease resulted from the exclusive use of blood from voluntary donors who have been tested for a hepatitis-associated antigen (HB Ag) believed to be part of the hepatitis virus.

Posttransfusion hepatitis has long been a risk for patients who receive multiple blood transfusions during surgery or for other reasons. In earlier research on this problem, Clinical Center and other investigators showed that patients receiving blood from commercial sources have an increased incidence of hepatitis. Blood containing HB Ag also frequently produces the disease, studies indicated.

As a result, the Clinical Center halted the use of commercially obtained whole blood--often purchased from drug addicts and others at high risk of contact with the hepatitis antigen--and initiated a program to screen all donor blood for HB Ag. This screening program is one of the first of its kind in the country.

In this screening program, scientists use an adapted counterelectrophoretic test which is based on the fact that HB Ag and the antibody produced to fight it are attracted to opposite electrical charges. Serum from a donor is placed in one well on an agar plate and serum containing antibody to HB Ag in an adjoining well. Electrical current is then applied.

(more)

The antibody migrates to the negative pole. If antigen is in the donor's serum, it will migrate to the positive pole. Where they meet--about halfway between the two wells--a precipitate forms leaving a white line.

Despite these precautions, some posttransfusion hepatitis continues to occur. Scientists at the Blood Bank attribute this to HB Ag in amounts too small to detect by present methods and to infection by other viruses.

Thus, in an effort to further decrease the frequency of posttransfusion hepatitis, the scientists at the Blood Bank are evaluating a radioimmune assay. In this more sensitive test, HB Ag is detected by radioactive marker. Although it takes longer, preliminary results indicate that this method detects hepatitis virus missed by counterelectrophoresis. If this proves true, the radioimmune assay will be used to screen all blood donors and counterelectrophoresis will be employed only when time for the newer test is not available.

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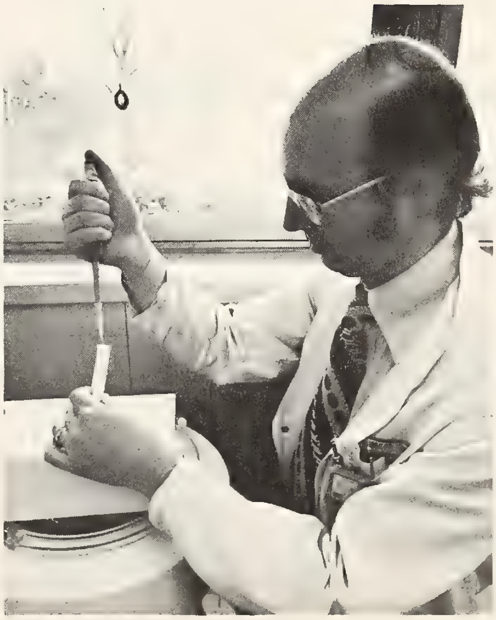
Blood Bank (Cont'd)



(Clockwise from top, left): Blood Bank technologist Holly Smith places a tube of donor whole blood in a centrifuge where it is "spun down" leaving serum at the top. For the counterelectrophoresis test, technologist Libbie Baldwin places a drop of donor serum in one well of a glass plate and serum containing antibody in an adjoining well. Up to 30 samples can be tested on one plate. The radioimmune assay, demonstrated by Harvey Alter, M.D., employs commercially prepared plastic tubes coated on the bottom with hepatitis antibody. Serum from donors is added and the tubes are incubated for 16 hours. If antigen is present, it will stick to the antibody. The tubes are washed to remove any loose antigen and more antibody--this time labelled with radioactive iodine--is added. The labelled antibody will stick to any antigen in the tube, sandwiching it against the antibody coated on the bottom. If no antigen is present, the labelled antibody remains free and is subsequently washed off. After washing, the tubes are placed in a machine that, like a sophisticated Geiger counter, records any radioactivity. Up to 300 samples can be recorded and the results printed out overnight. Total time: 24 hours. (NIH Photos #1016, #1017, #1018)

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Research Advances

CARRIERS MAY SPREAD INFECTIOUS "MONO"

Infectious mononucleosis--popularly known as the "kissing disease"--may be spread primarily by people who carry the infectious agent in their throats for months after their clinical disease has disappeared. This is one of the conclusions from a study carried out by researchers at the Yale University School of Medicine.

In the study, supported in part by the National Institute of Allergy and Infectious Diseases, the scientists also found convincing evidence that the causative agent of infectious "mono" is the Epstein-Barr virus (EBV). The virus, originally isolated from tissues of patients with Burkitt's lymphoma, has been suspected for some time as being the cause of mono.

In the Yale experiments, George Miller, M.D., and his associates took throat washings from 25 patients with definite cases of infectious mononucleosis and from 17 control patients. The investigators inoculated samples of the throat washings in an established line of human umbilical cord leukocytes (white cells).

Throat washings from 24 of the mono patients transformed the leukocytes into cells with unlimited growth potential in culture. Leukocytes inoculated with known EBV also transformed the leukocytes. Throat washings from the control group, however, did not transform the leukocytes.

According to Dr. Miller and associates, two lines of evidence indicate strongly that the transforming agent present in the throat washings of mono patients is the same as EBV and that this is the cause of infectious mono.

(more)

First, the investigators detected virus-specific antigens in the leukocytes that were transformed by the throat washings and EBV. Second, they found that the transforming activity of the throat washings is destroyed by antibody to EBV.

The unexpected finding of the study is that the investigators found the transforming agent in the throat washings for prolonged periods after the patients had acute infectious mononucleosis. It was present regularly two to five months after clinical illness. In one case, they detected the agent 16 months after the disease had occurred.

The presence of a persistent carrier state of EBV may explain why it has been so difficult to trace transmission of infectious mono on a case by case basis. These findings lend further support to the hypothesis that the disease is spread by the oral route, through intimate contact such as kissing.

This study was reported in the February 1, 1973 issue of the *New England Journal of Medicine* by Dr. Miller, James C. Niederman, M.D., and Linda-Lea Andrews, Yale University School of Medicine. The investigators also received support from the National Cancer Institute.

#

Research Advances

GRANTEES SUGGEST NEW METHOD FOR PREVENTING MENINGITIS

A new method for preventing meningococcal meningitis is suggested by research reported by National Institute of Allergy and Infectious Diseases grantees.

Drs. L. Barth Reller, Bob Roy MacGregor, and Harry N. Beaty, at the University of Washington, Seattle, have found that, in some persons, infection with non-disease-producing strains of the meningococcal organism stimulates the production of cross-reacting antibodies that can kill other strains known to be pathogenic. This raises the possibility of stimulating protective antibody production in high-risk groups (such as military personnel) by deliberately exposing individuals to non-disease-producing strains of meningococci.

The meningococcal organism occurs in several distinct immunologic strains and in others that, as yet, cannot be serologically identified and are known as nongroupable (NG).

An important aspect of meningococcal meningitis is the carrier state--the condition in which apparently healthy individuals harbor various strains of the bacteria. Past studies have usually been concerned with the strain carried, the length of time it can be isolated from the nose and throat, and environmental factors affecting the carrier rate. Only recently has research been concerned with the host's immunological response to bacteria carried in the oral cavity and to the role these organisms may play in development of natural immunity to meningococcal disease.

(more)

For eight weeks, the University of Washington scientists examined a company of military recruits at Fort Lewis, Washington, for the presence of meningococcal organisms. The isolation of NG strains for meningococci from 38 carriers in this company provided an unusual opportunity for Dr. Reller and his associates to assess the potential role of these generally nonpathogenic meningococci.

The scientists found newly developed or significantly increased cross-reacting bactericidal antibody to one or more virulent strains in 76.3 percent of the 38 recruits studied. Additional information obtained by the investigators suggested that the cross-reacting bactericidal antibody was not due to acquisition of undetected pathogenic meningococci. Antibody to the original NG strain and to pathogenic strains appeared simultaneously in the carriers.

Dr. Reller and associates published a report of their findings in the January 1973 issue of *The Journal of Infectious Diseases.*

#

Research Advances

IN THE LITERATURE:

Journal of Oral Surgery, October 1972

RESEARCHERS OFFER HOPE FOR REBUILDING JAWBONE--A National Institute of Dental Research-supported research team at the Boston University School of Graduate Dentistry offers hope for denture wearers whose appliances are unsatisfactory because too little bone remains to hold them securely.

Recently, Herbert Wells, D.M.D., of Boston University and Ramesh Narang, D.Sc., (now at the University of Illinois) and Daniel M. Laskin, D.D.S., also at the University of Illinois, reported that the specialized alveolar bone ridge which supports teeth and which often resorbs or disappears under pressure from dentures, can be stimulated to reform in dogs.

According to Dr. Wells, the hard outer shell (cortical) of dog bone was first treated to remove its mineral and then the remaining bone matrix was carved to the desired height and shape of the new ridge. The soft tissue of other, unrelated dogs was split to expose the jawbone and the flexible piece of matrix was fitted on top of the thin place. Then, the soft tissue was sewed back over the graft.

Dr. Wells reports that 16 weeks later scavenger cells had gradually removed the graft material while new bone, following the matrix framework, had entirely replaced the graft. The investigators saw no signs of rejection so long as they used only the cortical shell of bone for the graft. Previous experiments have shown that the inner (cancellous) layer of bone is rejected whether it is demineralized or not.

(more)

Demineralized cortical bone has also been used successfully in animals to repair bone defects around diseased tooth roots, and to fill in gaps in broken leg bones.

After further animal studies have established safety procedures, Dr. Wells' group plans to adapt the technique to selected patients. The investigator points out that it is not hard to get and store a good supply of human bone. Such bone, treated to remove its mineral, is easy to carve into any desired shape. Moreover, the use of bone matrix requires only one operation, while previously the only successful bone grafts have necessitated taking bone elsewhere from the patient at a cost of twice the time, discomfort, risk of infection, and expense.

For additional information about Dr. Wells' work in bone growth, see *News from NIH*, September 15, 1971.

#

NEWS & FEATURES From NIH March 25, 1973

Photo Feature

LABORATORY OF VISION RESEARCH SCIENTISTS STUDY DISEASE PROCESSES AND EYE FUNCTIONS

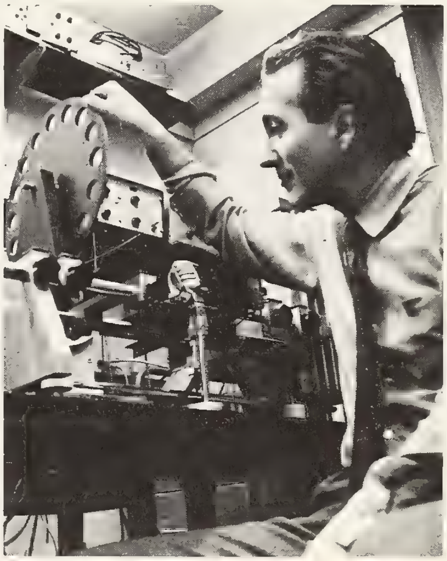
The National Eye Institute's (NEI) Laboratory of Vision Research plans and conducts fundamental laboratory research on the visual system. Major emphasis is placed on projects that will lead to an understanding of a disease process or how a particular part of the eye functions. Jin H. Kinoshita, Ph.D., heads the Laboratory, which during the past year began operating in newly renovated facilities on the NIH campus. The Laboratory is divided into four sections: Physiology, Experimental Embryology, Biochemistry, and Experimental Pathology.

(more)

Laboratory Chief, Dr. Jin H. Kinoshita, who is Acting Head of the Section on Biochemistry, demonstrated his tissue culture procedure for animal and human lenses in the study of cataract development. Because the lens is encapsulated and has no blood supply or nerves, it is relatively simple to remove and place it in an artificial environment and maintain it for long periods of time. A number of cataracts can be reproduced in lens culture. Currently, Dr. Kinoshita is studying the development and prevention of cataracts associated with diabetes and galactosemia. (NIH Photo #1019)

Vision Laboratory (Cont'd)

The Section on Experimental Embryology, headed by Alfred J. Coulombre, Ph.D., is devoted to the study of ocular development. Here, Dr. Coulombre and his wife, Jane L. Coulombre, focus attention on the "initiator layers" that are transiently produced by and deposited beneath several epithelia of the embryonic eye at specific times during development. Initiator layers are thought to be centrally involved in differentiation and morphogenesis, not only in the eye, but also in most organs of the body. **Next month,** *Dr. Coulombre will speak at the second FASEB conference, "Biological Transmission of Information".*



Toichiro Kuwabara, M.D., Ph.D., (left) Head of the Section on Experimental Pathology, conducts investigations to understand the structure of the eye in both normal and pathologic conditions, such as retinal and corneal diseases and glaucoma. He has found that prolonged and continuous exposure to light may lead to degeneration of the retina. Peter Gouras, M.D., (right) Head of the Section on Physiology, is undertaking the recording of single cell responses in the monkey retina and brain in order to understand how color and pattern vision is processed by the brain. Dr. Gouras uses moving slits of different colors and brightness to study aspects of the function of single nerve cells. (NIH Photos #1021, #1022)

Vision Laboratory (Cont'd)

Studies on the biosynthesis of rhodopsin are being conducted by Paul J. O'Brien, Ph.D., (left) Section on Biochemistry. Dr. O'Brien's studies are contributing to an understanding of the normal degeneration and renewal of the photo-receptor outer segment of the rods and may aid in further understanding of abnormal degenerative processes. (NIH Photo #1023)

David A. Newsome, M.D. (middle photo) Section on Experimental Embryology, studies the developmental interactions of embryonic chick retinal pigmented epithelium. He will be able to follow the interactions in the laboratory as they would occur normally in the eye. (NIH Photo #1024)

W. Gerald Robison, Jr., Ph.D. (bottom, left), Section on Experimental Pathology, demonstrates the scanning electron microscope which permits the scientist to observe the fine structure of cells in three dimensions. In this laboratory, it is being applied to the study of normal and pathological lenses, corneas, and other ocular tissues. (NIH Photo # 1025)

Gerald J. Chader, Ph.D. (bottom, right), Section on Biochemistry, investigates the measurement of enzyme properties and their distribution in the retina. He hopes to gain a better understanding of the biochemical changes evoked by light striking the retina. (NIH Photo #1026)

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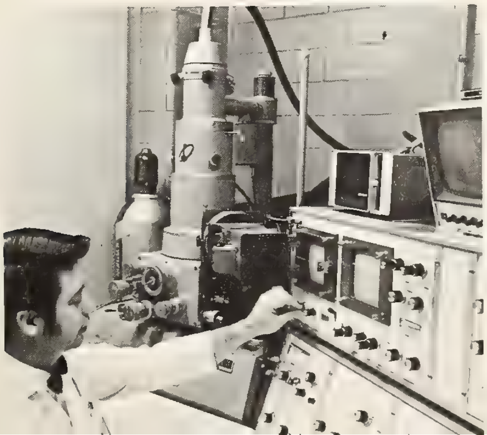

News-Feature

TREATMENT USED IN HEAD INJURY MAY ACTUALLY HARM THE PATIENT

Procedures commonly used to treat head injury have never been tested adequately to prove if they are helpful. In some instances, these procedures even may be harmful.

These findings come from scientists who participated in a recent National Institute of Neurological Diseases and Stroke (NINDS) Head Injury Center Research Workshop held in Washington, D.C. on February 24, 1973.

According to Ayub K. Ommaya, F.R.C.S., head of the Applied Research Section of the NINDS Surgical Neurology Branch and chairman of the workshop, "Since we don't yet know what brain changes mean following injury, we don't know how best to treat the patient." Known changes include those in cerebral blood flow, intracranial pressure, and hormone levels.

Workshop participant Thomas W. Langfitt, M.D., of Philadelphia General Hospital, explained, "We haven't been able to study effects of specific therapies in man because the head injury patients are acutely ill. So we try everything."

However, new animal models developed by Dr. Ommaya and associates now may help answer many crucial questions.

One question concerns urea therapy, one of the four measures doctors use to treat acute head injury. New evidence presented by Dr. Stanley I. Rapoport, M.D., National Institute of Mental Health Laboratory of Neurophysiology, indicates that urea, while decreasing brain edema, may actually be detrimental. Urea lures water out of the brain by shrinking cells which

(more)

normally pack together to form an impenetrable barrier between the brain and blood vessels. "But," he said, "there is strong indication that it may allow minute, potentially harmful constituents from the blood to enter the brain, and, conversely, to allow other particles, to drain out of the brain." Additionally urea itself can pass through the barrier in large enough quantity to induce water back into the brain.

"Few patients have irreversible brain damage caused by primary mechanical injury to the brain stem," Dr. Ommaya said. "Instead, irreversible damage is often a secondary result caused by after-effects. That's why proper treatment is so crucial."

The other three methods used to treat acute head injury are hypothermia (cooling the brain), steroid administration to reduce pressure, and carbon dioxide reduction.

But some scientists seriously questioned the value of measuring intracranial pressure and blood flow, since to date, measurements do not reflect the severity of the injury. Therefore, it is not yet clear just what these changes signify, and, measuring them introduces the risk of infection.

For instance, Derick Bruce, M.D., of the University of Pennsylvania, presented evidence that decreased blood flow may trigger the brain's own defense mechanisms. His studies indicate that a reduced cerebral blood flow is accompanied by a reduced demand by the brain for glucose and oxygen. Therefore, a lowered blood flow would not initially be dangerous. This observation coincided with basic studies on the brain's oxygen control

(more)

conducted by Haim Bicher, M.D., Ph.D. and Melvin Knisely, Ph.D., of the Medical University of South Carolina. Their studies suggest that brain tissues have receptors to regulate oxygen supply to its demand, like a thermostat regulates heat for a house.

"If this is so," Dr. Ommaya said, "we need to learn how we can influence this regulation."

Fred Plum, M.D., Cornell University Medical Center, presented evidence indicating that harmful effects are produced when anoxia (reduced oxygen) is accompanied by ischemia (reduced blood flow) allowing build-up of metabolic by-products.

Hormonal changes also may alter brain functions. Jonathan Costa, M.D., Ph.D., of the NINDS Laboratory of Neuropathology and Neuroanatomical Sciences said, "Our studies indicate that norephinephrine (a chemical message transmitter) is blocked before it can be transmitted along the nerve."

According to Dr. Ommaya, "the animal models have shown that while EEG's (measurement of brain wave activity) do not adequately indicate the extent of brain damage, brain waves produced by stimulating various parts of the body are excellent."

He expects that animal models soon will provide crucial information on brain changes and effects of various treatments.

Scientists stressed the need for clinical studies defining the natural history of head injury. Bryan Jennett, M.D., Glasgow, said, "A scale is needed to measure neurological outcome in survivors. We can't assume everyone who gets better, past the vegetative state, has recovered. 'Return to work' is a misleading criteria for recovery."

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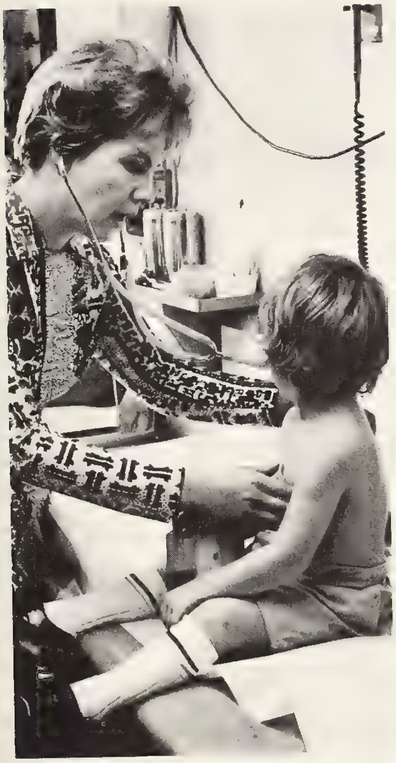
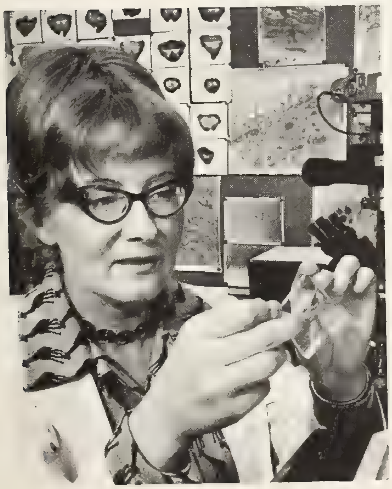
Photo Feature

Wisconsin Grantees...

SCIENTISTS SEEK SOLUTIONS TO DIVERSE HEALTH PROBLEMS





In separate research studies at the University of Wisconsin Medical School, scientists search for answers to a variety of health problems. Patricia Ann Joo, M.D. (upper left), examines a young cancer patient. Dr. Joo's research on the therapy of children with leukemia and malignancy is supported by the National Cancer Institute. (NIH Photo #1027) Hanna M. Sobkowicz, M.D., Ph.D. (lower left), develops central nervous tissue in culture. Dr. Sobkowicz receives support from the National Institute of Neurological Diseases and Stroke. (NIH Photo #1028) The National Institute of Child Health and Human Development supports Margaret W. Orsini, Ph.D. (upper right) as she studies the sequence of events in implantation of the ovum. (NIH Photo #1029) June E. Osborn, M.D. (lower right), associate professor of medical microbiology and pediatrics, performs cytomegalovirus research under a grant from the National Institute of Allergy and Infectious Diseases. (NIH Photo #1030)

Medical News Tip

NHLI STUDIES RESPIRATORY DISEASES--Lung diseases account for an estimated 150,000 deaths each year in this country and cause 60 million days lost from work and 40 million days of bed-restricted activity, and cost the economy approximately $6 billion in lost productivity, wages, and costs of medical care.

The National Heart and Lung Institute's (NHLI) Division of Lung Diseases is working to reduce these figures. Some topics currently under study by the Division include:

- the chemical structure and processes of the lung and how these are modified by lung diseases
- lung diseases resulting from chronic exposure to dusts, fumes, and vapors in certain occupations, to air pollution, or to cigarette smoking
- lung damage resulting from drug reactions or radiation
- respiratory distress syndrome, including hyaline membrane disease--the leading cause of death in the newborn

For additional information about the Division of Lung Diseases, contact: NHLI Information Office, Landow Building, Room C-918, Bethesda, Maryland, 20014, Phone (301) 496-4236. A copy of a recently-published report on respiratory diseases is also available.

#

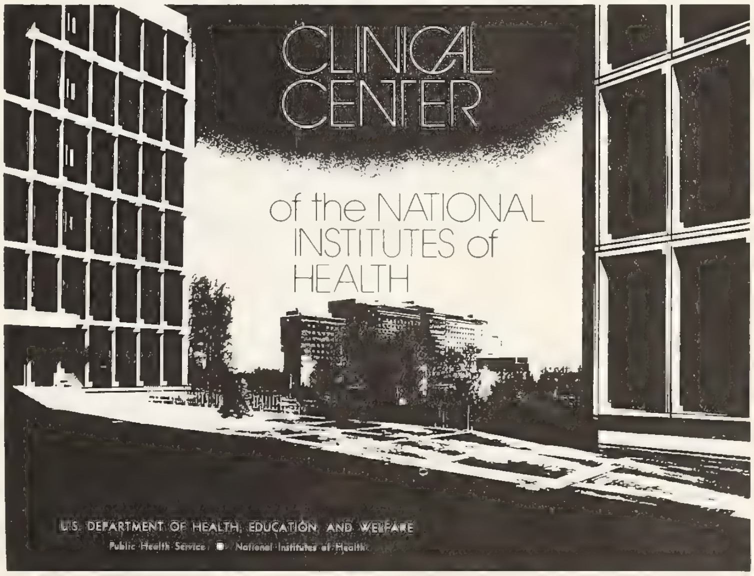
New Publication:
The Clinical Center

The Clinical Center, a 14-story, 516-bed hospital located on the NIH campus, is designed to bring scientists in laboratories into close proximity with clinicians caring for patients so that investigators and physicians can collaborate on problem diseases.

The mission of the Clinical Center is to provide specialized forms of hospital care necessary for Institute studies. Patients receive immediate benefits from new advances in medical care techniques. Illnesses under study range from the common cold to cancer.

Programs are conducted in the Clinical Center by the various NIH Institutes and the National Institute of Mental Health, with each Institute planning and conducting its own research. When an aspect of a disease is selected for study, the methods of approach are determined by a research team, which may include scientists from more than one Institute and from other research organizations.

The Clinical Center, an illustrated brochure, describes the research facility and explains its mission, patient admission procedures, and history. Science writers and editors may obtain a free copy of this publication from: Clinical Center Information Office, Bldg. 10, Room 1N-248, NIH, Bethesda, MD 20014, Phone (301) 496-2563.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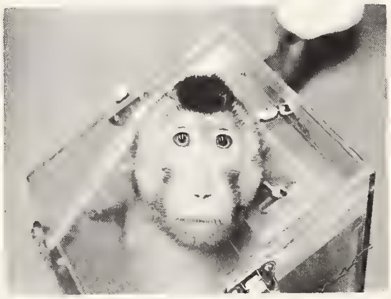

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SPECIAL SUPPLEMENT: *NIH Portfolio on Asthma and Allergic Disease Centers*

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NEWS & FEATURES From NIH April 10, 1973

Research Advances

AEROSOL PROPELLANT GASES CAN BE TOXIC TO THE HEART

A National Heart and Lung Institute grantee has found that aerosol propellant gases, previously described as "inert", are rapidly acting and potent cardiac toxins. Since their introduction 40 years ago as refrigerants, these fluoroalkane gases used to propel aerosols have been considered harmless.

Willard S. Harris, M.D., of the University of Illinois College of Medicine, Chicago, first discovered this toxicity in mice and has now confirmed the findings--either in vitro or in vivo--in rats, dogs, cats, monkeys, and man. Dr. Harris believes that the possibility of these gases being harmful to frequent aerosol users--either acutely or chronically--requires further study.

Aerosols, defined by Dr. Harris and the aerosol industry as products packaged under pressure which can be discharged from their containers by that pressure, contain three principal components: propellants, solvents, and active ingredients, as well as perfumes and emollients. The most commonly used aerosol propellants are the fluorinated hydrocarbons, popularly known as Freons.

During the past five years, 140 healthy youths have unexpectedly died minutes after trying to become intoxicated by inhaling the gas from aerosol propellants. The sudden nature of these deaths and the negative autopsy findings suggested to Dr. Harris that the fatal mechanisms might be cardiac.

(more)

In his first study in October 1970, the grantee showed that the fluoroalkane gases were toxic to the mouse heart. From these results, he predicted that the propellant gases also would be found toxic to the cardiovascular system in several different ways, depending in part on the species under study. His present studies have shown exactly this.

Dr. Harris and associates found that the gases enter the blood of monkeys, cats, and dogs after inhalation and, despite adequate oxygenation, have a spectrum of cardiovascular toxic effects. The gas directly depressed contractility in rat, cat, dog, and human myocardium; lowered arterial blood pressure in the monkey, cat, and dog; and rapidly induced ventricular arrhythmias in awake or anesthetized monkeys.

The scientist also reports detecting fluoroalkanes in the blood of humans after inhalation of aerosol propellants. His experimental studies to date suggest that ventricular tachyarrhythmias, bradyarrhythmias, acute heart failure, arterial hypotension, and asphyxia may contribute singly or in combination to the sudden death of youths who deliberately inhale aerosol propellants. A definition of the mechanism by which the gases exert these toxic actions is of primary importance to Dr. Harris.

Based on his study findings Dr. Harris believes that it is necessary to determine the quantities of these gases entering the blood of people who are frequently exposed to them. He also suggests determining whether or not certain conditions such as asthma, heart failure, coronary artery disease, or heart block might increase susceptibility or diminish tolerance to the

(more)

toxic effects of these gases. It seems likely to the investigator that people may have individual differences in their sensitivities to one or more of these toxic effects.

Although no evidence for long-term toxicity has appeared to date, Dr. Harris suggests measuring the amounts of gas entering the blood of people who frequently use aerosols. Also, he recommends functional, biochemical, and epidemiological studies to detect any evidence of harmful effects resulting from this exposure.

A full report of this investigation appears in *Archives of Internal Medicine*, January 1973.

#

Research Advances

NEUROSCIENTISTS DEVELOP TECHNIQUE FOR STUDYING PROCESSES OF MEMORY

A new interpretation of how two major brain structures function in memory transfer has been developed by National Institute of Neurological Diseases and Stroke grantees.

Their studies indicate that while the corpus callosum is capable of extracting memorized information from one side (hemisphere) of the brain for use by the other, the anterior commissure can permanently transfer such information from one hemisphere into the other.

Robert W. Doty, Ph.D., professor of physiology and psychology at the University of Rochester Center for Brain Research, and his associate, Nubio Negrao, M.D., proposed that the corpus callosum (which is a very rich system of cross connections between the two hemispheres) has two unique functions in memory. First, it allows each half-brain to have access to memories which are stored in the other half. Second, it prevents memories from being stored in both halves of the brain. With this arrangement, the number of memories which can be stored is double what would be if each side stored the same memory; yet, the memory is available to the other half through these cross connections in the corpus callosum.

Although scientists have known for years that right-handed people store memory for language primarily in the left half of the brain, they had not realized that such one-sided storage may be related to the functioning of the corpus callosum. It is still not known what determines which half of the brain will store what memory.

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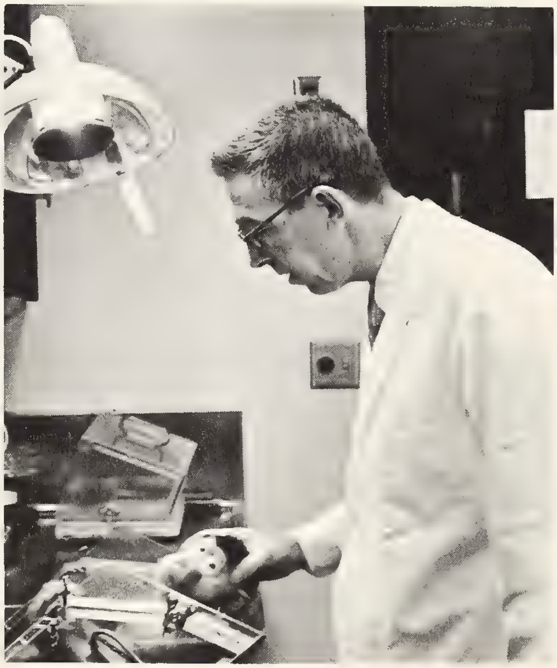
Drs. Doty and Negrao suggest that this may at first be determined by which half brain receives the most information from the senses.

In their experiments using electrical stimulation through tiny electrodes implanted in a monkey's brain, they could choose at will which half of the brain would store the memory. From similar stimulation in man, it can be inferred that the monkey probably saw a very small spot of light when the stimulation was on. The monkey learned that this stimulation meant food or fruit juice was available.

If the animal had first learned this as a result of stimulation of the right half of the brain, it immediately "remembered" the significance when the corresponding left half of the brain was stimulated. However, the memory for this remained in the initially stimulated right half brain. When the corpus callosum was cut, the left brain was totally ignorant of the significance of the stimulation, whereas the monkey's response to stimulation of the right half brain was unaltered.

These experiments showed that the corpus callosum connecting the two halves of the brain could put one half "in touch" with a memory between the two halves, but that the memory was not transferred.



Dr. Robert W. Doty prepares a monkey for studies of memory transfer. Dr. Doty is professor of physiology and psychology at the University of Rochester Center for Brain Research. (NIH Photo #1031)

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Drs. Doty and Negrao obtained an entirely different result when they did the same experiment using a small bundle of cross connections in the anterior commissure (a smaller mass of connections). In this possibly more primitive system they found that the memory actually was transferred into the nonstimulated half of the brain.

According to the investigators, these are then two clearly localized pathways in the brain which handle memory in distinctly different ways. The corpus callosum can only command "readout" of a memory and cannot (or at least did not in these experiments) induce memory storage of "write in." The anterior commissure, on the other hand, possesses the latter capability and thus for the first time will allow direct analysis of the time course and location of this process.

Knowing where to look, the investigators now believe they can begin asking questions on how memory is stored and activated.

#

Research Advances

STUDIES LINK PROSTATITIS TO SERIOUS KIDNEY DISEASE

Experiments in male rats have revealed that infection of the prostate may lead to the development of pyelonephritis--a serious kidney disease. Physicians have suspected for some time that chronic bacterial prostatitis might be a common cause of recurrent urinary tract infections in men, but experimental evidence has been lacking.

Since acute uncomplicated pyelonephritis rarely leads to death, knowledge of the disease process is based almost entirely on experimentally-induced infections in laboratory animals.

Drs. Arthur M. Friedlander and Abraham I. Braude, University of California School of Medicine, San Diego, report that in their continuing study of experimental pyelonephritis in the rat they have been impressed by the frequent appearance of prostatitis in male animals. These studies are supported by grants from the National Institute of Allergy and Infectious Diseases and the National Heart and Lung Institute.

When the grantees inoculated male rats with the bacterium *Proteus*, they found that nearly all animals developing prostatitis had associated pyelonephritis. Kidney infection was rare if prostatitis was not present. Moreover, rats were significantly protected against kidney disease if they were castrated long enough before bacterial challenge for the prostate to have been destroyed.

These findings were unexpected since previous reports have suggested that the prostate plays a protective role in pyelonephritis, due to the antibacterial activity of prostatic secretions. The California scientists believe that

(more)

prostatitis occurs when this activity is overwhelmed by the size of the inoculum and other experimental factors. The prostate may then serve as a focus of infection and obstruct normal urine flow, leading to infection of the urinary tract.

Direct inoculation of bacteria into the prostate did not cause pyelonephritis in the rats. The investigators stress, therefore, that prostatic infection, by itself, is not sufficient to cause progressive urinary tract infection. Other factors are involved, including some degree of bladder infection.

Drs. Friedlander and Braude report their findings in the *Journal of Infectious Diseases*, December 1972.

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NEWS & FEATURES From NIH April 10, 1973

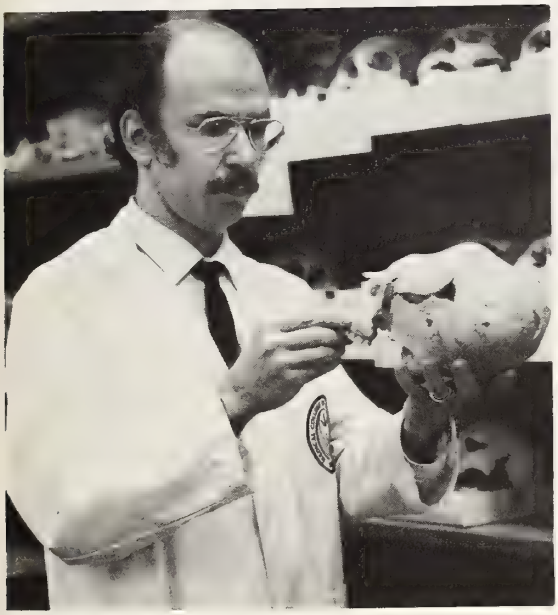
Photo Feature

"AUTOPSIES" UNCOVER ROOTS OF MODERN MAYA DISEASES

A biomedical anthropologist at the Medical College of Ohio, Toledo, has performed an unusual series of "autopsies" in order to understand the history of modern day health problems of the Maya Indians of Central America.

Frank P. Saul, Ph.D., associate professor of anatomy at the college, has studied thousands of bones collected by various expeditions to the ruins of Maya cities, seeking signs of injuries and disease. He calls his study "osteobiography": the determination of an individual's life history from anatomic changes in his bones. The NIH Division of Research Resources provided funds for these studies through a General Research Support Grant to the Medical College.

Although the Maya Empire created one of the major civilizations of the Western Hemisphere, it disintegrated some 500 years before the Conquistadores arrived in the New World. Scientists have long tried to determine the health, food supply, and mysterious fate of these people in relation to the disease-ridden modern Maya.



Frank P. Saul, Ph.D., associate professor of anatomy at the Medical College of Ohio, Toledo, examines a reconstructed Maya skull.
(NIH Photo #1032)

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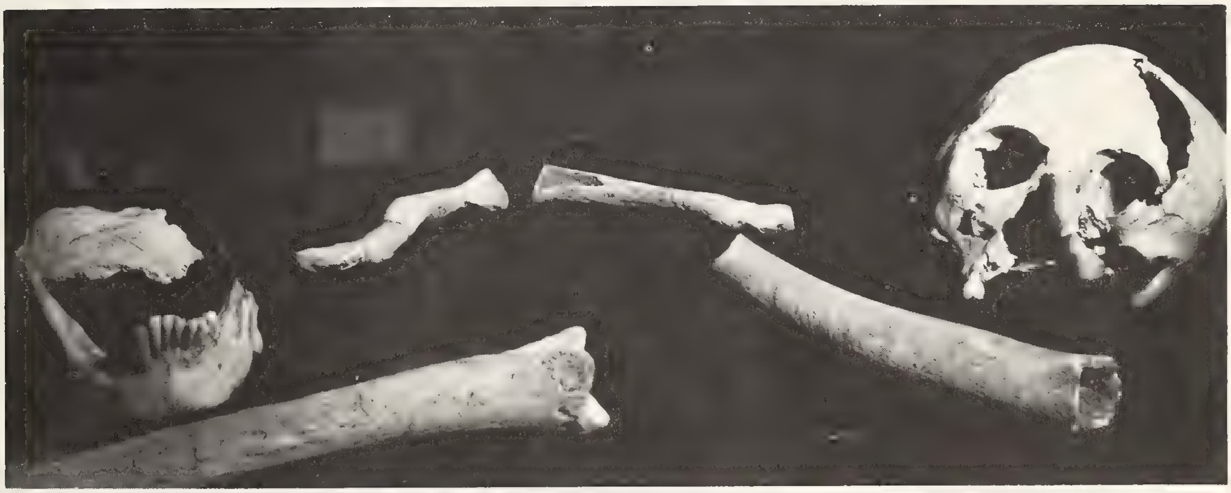
According to Dr. Saul, once a broken bone heals, it leaves clear evidence that the bone has knitted together and indicates that the individual lived long enough after the fracture to permit the bone to heal.

The evidence from Dr. Saul's osteobiographic analysis indicates that, contrary to some theories, the Maya were larger than their modern descendants but that they were wracked with injuries and disease. "I have found a great variety of disorders including healed fractures, bone inflammation, and a high incidence of other skeletal lesions," states Dr. Saul. "Malnutrition, parasitic infestation, and childhood infections were probably common," he adds. Since this is the first direct evidence that the Maya civilization encountered a food shortage and nutritional problems, the discovery endorses earlier theories that something caused the food supply to disappear.



Portions of Maya skeletal material show healed fracture of clavicle and lesions from yaws or syphilis. (NIH Photo #1033)

"The evidence of malnutrition in the Altar group could help explain the collapse of the Maya Empire in the 9th and 10th centuries, and the decrease in size of these people from ancient to modern times," Dr. Saul explains. "Furthermore, it provides new time depth for present day health problems in Central America. It would seem that many modern day health problems have their roots in 'ancient' civilization not 'modern' as was believed."

Dr. Saul's findings also question the belief that syphilis was first brought to the New World by Spanish expeditionary forces under Columbus, Pizarro, Balboa, and others.

According to the researcher, "Maya bones dating back to 745 A.D. and earlier show the typical lesions caused by syphilis or yaws." Although present techniques cannot distinguish between these two diseases, Dr. Saul says, "The documented pre-Columbian presence of these lesions could generate further controversy concerning the origin of the treponematoses (syphilis-like diseases)."

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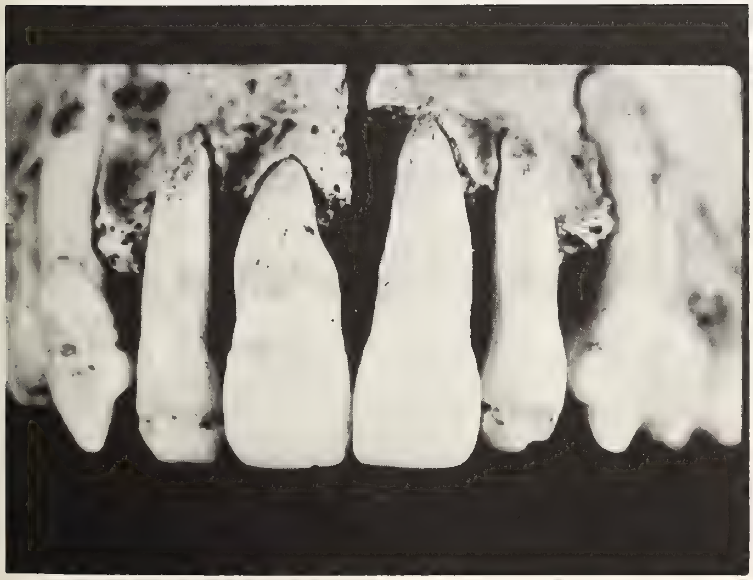

Dr. Saul found evidence of incomplete formation of the enamel (linear hypoplasia) in the skeleton of a male young adult. This resulted from growth interruption due to malnutrition or other severe illness at age three or four. Similar hypoplastic lesions occur in the deciduous teeth of modern Maya and are thought to be associated with infections during the first month of life.
(NIH Photo #1034)

Maya Diseases (Cont'd)

In addition to work on these bones from Altar de Sacrificios, Dr. Saul is also involved in comparable studies of skeletal remains from Seibal, another center of Maya culture. So far, the examination of the Seibal material appears to corroborate the findings at Altar, Dr. Saul says.

Fragments from a dig cover a workbench in the lab of Dr. Frank Saul of the Medical College of Ohio. Dr. Saul's study of morbidity and mortality of ancient and modern Maya is supported by a grant from the NIH Division of Research Resources. (NIH Photo #1035)

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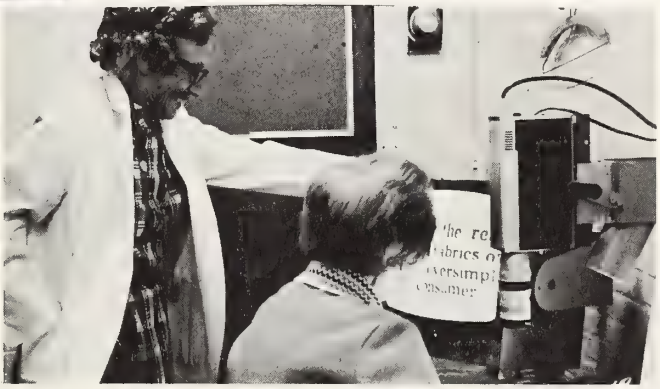
Photo Feature

At Johns Hopkins...

DRS. SLOAN AND CHARACHE ARE AMONG NIH GRANTEE SCIENTISTS

Louise Littig Sloan, Ph.D., a National Eye Institute grantee at the Johns Hopkins University School of Medicine, is developing psycho-physical tests for the study of visual functions in eye disease as well as aids for the partially sighted. At left, Dr. Sloan standardizes intensities on the tubinger-perimeter, an instrument which measures visual fields in light and dark as well as the rate of adaptation to darkness. Below, she shows a patient how to use a closed circuit TV reader. An associate professor emeritus, Dr. Sloan has been at the school since 1929. (NIH Photos #1036, 1037)



Patricia Charache, M.D., a National Institute of Allergy and Infectious Diseases grantee at Johns Hopkins, is an assistant professor of medicine and microbiology. The objectives of her work are to determine the role of cell wall defective bacteria in human disease. Above, Dr. Charache reviews an isolate with one of her students. At right, she stains slides in preparation for her studies. (NIH Photos #1038, 1039)

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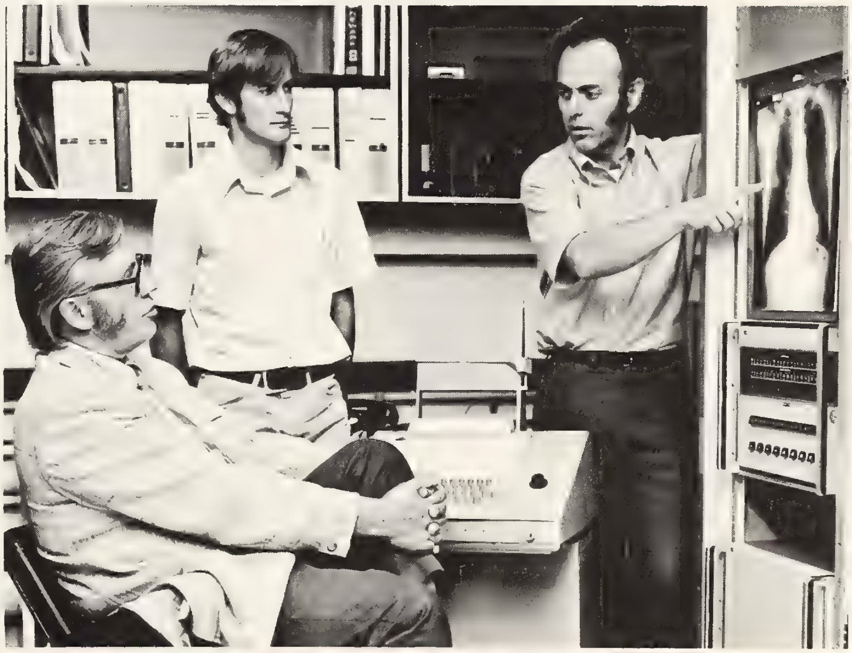
Photo Feature

COMPUTER READS HARD-TO-SEE IMAGES OF LUNG TUMORS ON CHEST X-RAYS

The lung tumor is one of the most common and important types of lesions in a chest radiograph. The contour of a lung tumor reveals much of the diagnostically significant information about the tumor's size, shape, and location.

Jack Sklansky, Sc.D., of the University of California School of Engineering at Irvine, is developing a computerized technique for detecting hard-to-see images of lung tumors on chest X-rays. The project is co-directed by B. J. O'Loughlin, M.D., chairman of radiological sciences at the University of California Medical School at Irvine. Their research is supported by the National Institute of General Medical Sciences.



Dr. Jack Sklansky points out lesion to Dr. B. J. O'Loughlin (left) and Dana Ballard. (NIH Photo #1040)

The scientists use a sensitive electronic scanner to detect slight variations of light on the X-ray. A computer then manipulates the highly accurate reading to provide an outline of the tumor image.

According to Dr. Sklansky, highly-trained radiologists

(more)

Computer X-rays (Cont'd)

using visual techniques can miss up to 25 percent of tumor images on chest radiographs. He and Dr. O'Loughlin have developed a computer program which can detect the complete size and shape of a tumor from an image which is incomplete or confused by an overlay of ribs, blood vessels and lung tissue.

The researchers are also examining the technique as a means for accurately counting blood cells in microphotographs and for detecting nodules in isotope scans of livers.

#

Medical News Tip

AMERICAN-SOVIET AGREEMENT--The U.S.-U.S.S.R. Joint Committee for Health Cooperation concluded its second annual meeting March 30 and signed a memorandum of agreement calling for continued and strengthened collaboration in three major areas: heart disorders, cancer, and environmental health.

The document was signed by Dmitri D. Venediktov, M.D., Deputy Minister of Health, for the U.S.S.R., and by Roger O. Egeberg, M.D., Special Assistant to the Secretary for Health Policy, for the United States.

The signing ceremony at the Fogarty International Center marked the conclusion of a successful five-day meeting and of the first full year of activity under a five-year agreement signed in Moscow last Spring.

Besides re-emphasizing the importance of the three areas in which collaborative efforts have already been started, the new agreement suggests that a program be developed on the organic basis of schizophrenia. Other areas of potential collaboration mentioned in the document are: arthritis, occupational health, delivery of health services, and medical communications.

Highlights of the progress reports presented to the Joint Committee included the fact that 101 Soviet and United States scientists visited and worked in each other's country for a total of 101 man-months over the past twelve months, a five-fold increase since the new agreement was signed in March, 1972.

For additional information contact: Mrs. Lois Meng, NIH, Building 31, Room 2C-12, Bethesda, Maryland 20014, Phone (301) 496-4625.

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New Publication:
So, I have the sickle cell trait

So, I have the sickle cell trait..., a new publication from the National Heart and Lung Institute (NHLI), is designed to answer a child's questions about sickle cell anemia. The booklet differentiates between sickle cell trait and sickle cell disease, and explains that the child with the trait does not have an illness.

This new publication was prepared for NHLI by Cynthia Kaufman, an educator, lecturer, and biology instructor at the University of Bridgeport, Connecticut, and aimed at the grade school child.

The child can carry the booklet (shown actual size at right) in his pocket for easy reference.

Science writers can obtain a copy of this booklet from:

NHLI Information Office
Landow Building, Room C-918
Bethesda, Maryland 20014
Phone: (301) 496-4236

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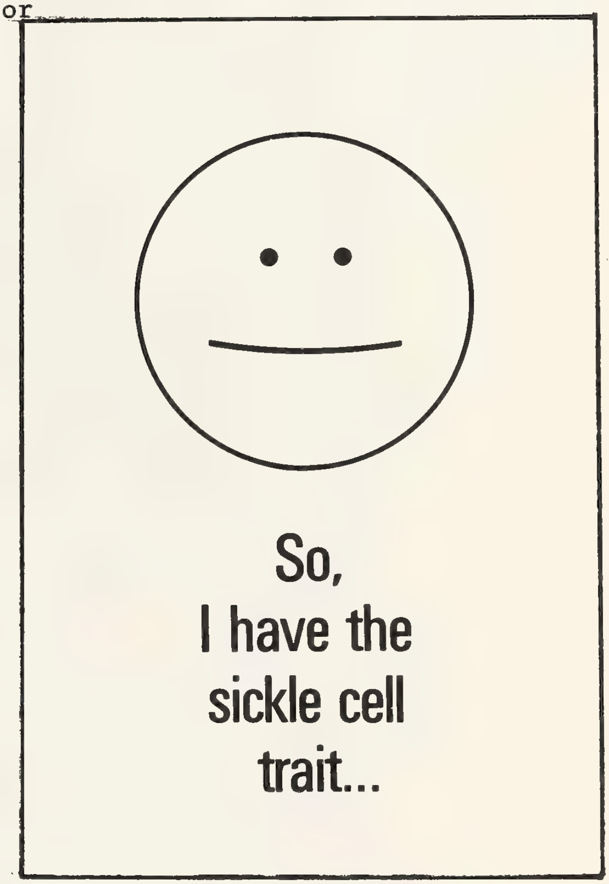

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NEWS&FEATURES FROM NIH

PORTFOLIO · ASTHMA AND ALLERGIC DISEASE CENTERS

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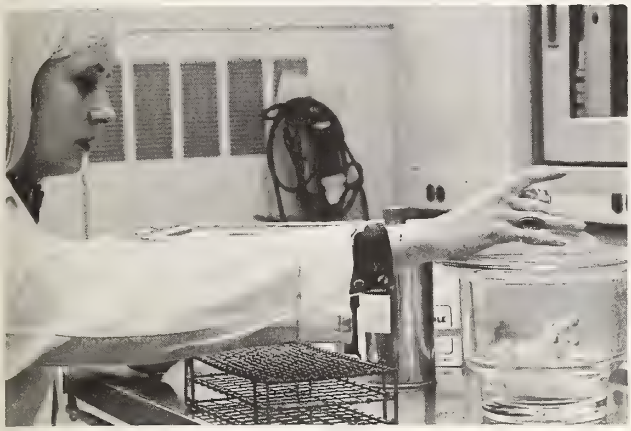

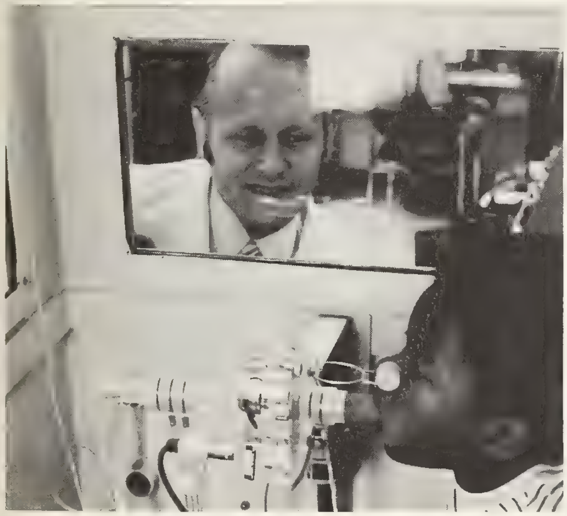

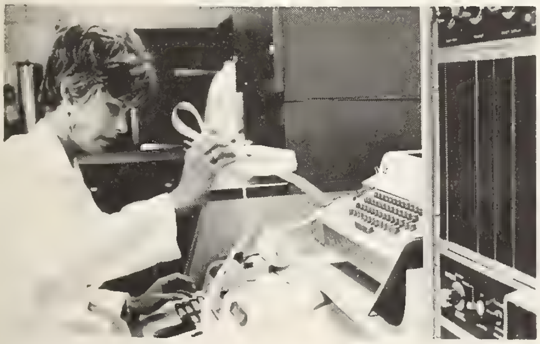

APRIL 1973

NEWS&FEATURES FROM NIH

NIH PORTFOLIO ON ASTHMA AND ALLERGIC DISEASE CENTERS....APRIL 1973

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE■Public Health Service■National Institutes of Health■Office of Information■Bethesda, Maryland 20014

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INTRODUCTION: NIH SUPPORTS ASTHMA AND ALLERGIC DISEASE CENTERS

This introduction was prepared with the assistance of William I. Gay, D.V.M. (left), Sheldon G. Cohen, M.D. (center), and Luz A. Froehlich, M.D., of NIH's National Institute of Allergy and Infectious Diseases (NIAID). Dr. Gay is Associate Director for Extramural Programs, NIAID; Dr. Froehlich is his assistant for clinical programs; and Dr. Cohen is Allergy Consultant. The National Institutes of Health is an agency of the U. S. Department of Health, Education, and Welfare.

In recent years, programs of the NIH's National Institute of Allergy and Infectious Diseases (NIAID) have reflected an increased interest in research on allergic diseases. Basic studies in immunology--long supported by the Institute--have provided findings which have opened the way for further studies designed to apply new knowledge to the benefit of the allergic patient.

(more)

Laboratory experiments, investigations in animals, clinical studies, scientific communication, and the development of research resources are all a part of the allergy research programs of NIAID. This research is carried out in Institute laboratories on the NIH campus, in industrial laboratories, and, most importantly, in a network of ten asthma and allergic disease centers.

Programs at the Asthma and Allergic Disease Centers involve studies of individuals primarily on an out-patient basis. Close coordination between basic and clinical research scientists in these Centers is expected to translate rapidly expanding knowledge of immunology into improved clinical allergy practice. Some of the areas studied at the Centers include immunologic factors involved in allergic diseases; the role of respiratory infections in asthma; analysis of immunologic, pharmacologic, environmental and psychologic variables as they contribute to the symptoms of asthma; and improved methods of treatment for asthma and other allergies.

Although allergic reactions can take various forms--such as nasal or bronchial problems, hives, eczema and other skin disorders--they all have a common immunologic basis. In all cases, an allergen (the allergy-causing substance) stimulates the allergic response, usually after repeated contact. Regardless of the form this response takes, it results from the formation of antibodies and the sensitization of certain cells in the allergic individual's body. Unlike the protective antibodies induced by a viral infection, allergic induced antibodies may actually harm the individual. Repeated contact with the allergen increases the distressing symptoms of allergy.

The goal of the NIAID effort is aimed at better diagnosis, prevention and treatment of allergic disorders. According to Dorland J. Davis, M.D., NIAID Director, "We hope the knowledge gained through our Asthma and Allergic Disease Centers program--and the exchange of information and ideas among scientists--will result in better care for those who suffer the debilitating effects of asthma and other allergies."

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ASTHMA AND ALLERGIC DISEASE CENTERS and CENTER DIRECTORS

Ann Arbor, MI	University of Michigan Medical Center, Dr. Kenneth P. Mathews, Director
Baltimore, MD	Johns Hopkins University School of Medicine, Dr. Philip S. Norman, Director
Bethesda, MD	National Institute of Allergy and Infectious Diseases, Allergy Unit, Dr. Allen P. Kaplan, Director
Boston, MA	Robert B. Brigham Hospital and Harvard Medical School, Dr. K. Frank Austen, Director
Buffalo, NY	State University of New York, Dr. Carl E. Arbesman, Director
Denver, CO	Children's Asthma Research Institute and Hospital, Dr. Elliott Middleton, Jr., Director
Denver, CO	National Jewish Hospital and Research Center, Dr. Richard S. Farr, Director
La Jolla, CA	Scripps Clinic and Research Foundation, Dr. John H. Vaughan, Director
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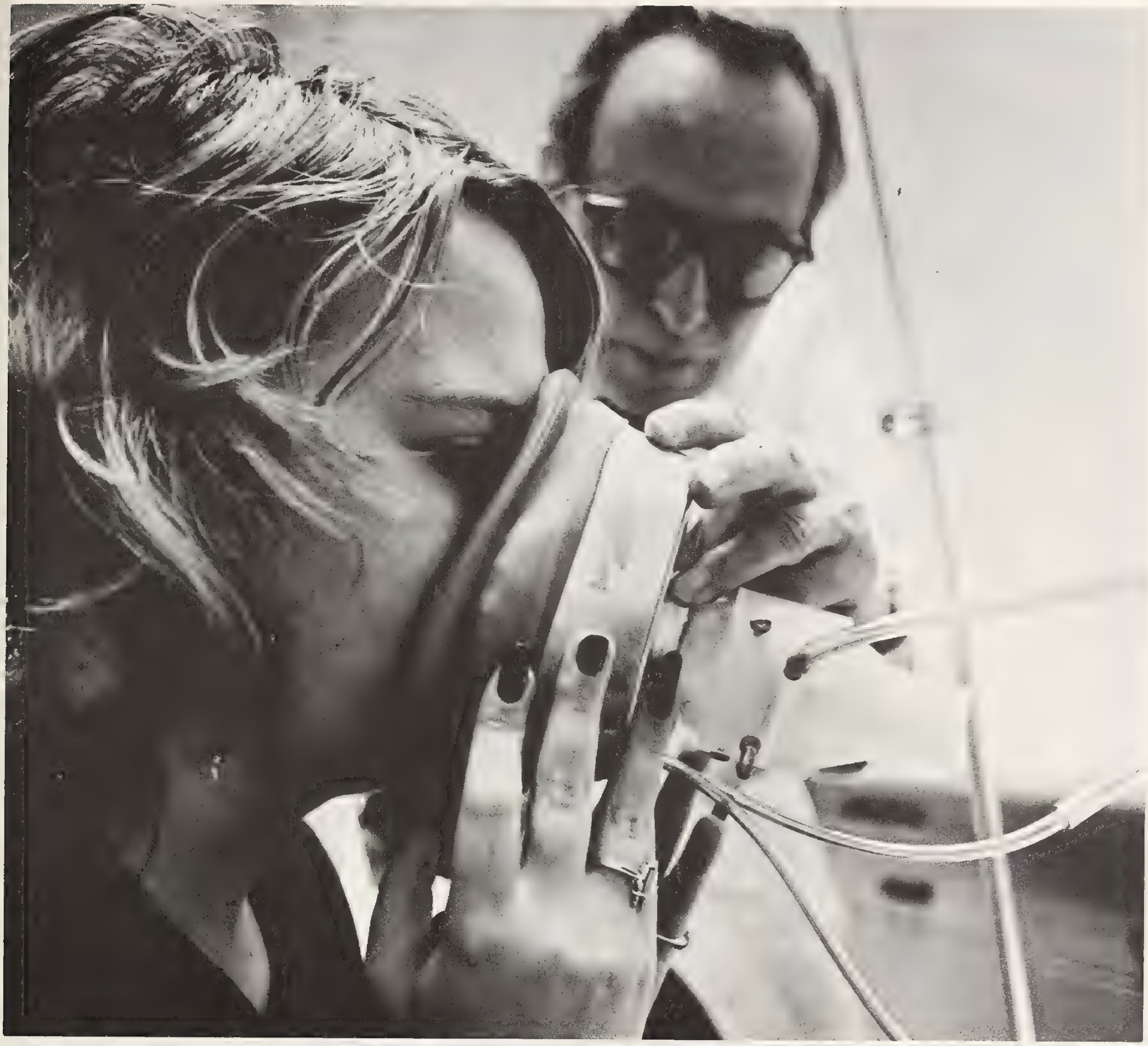
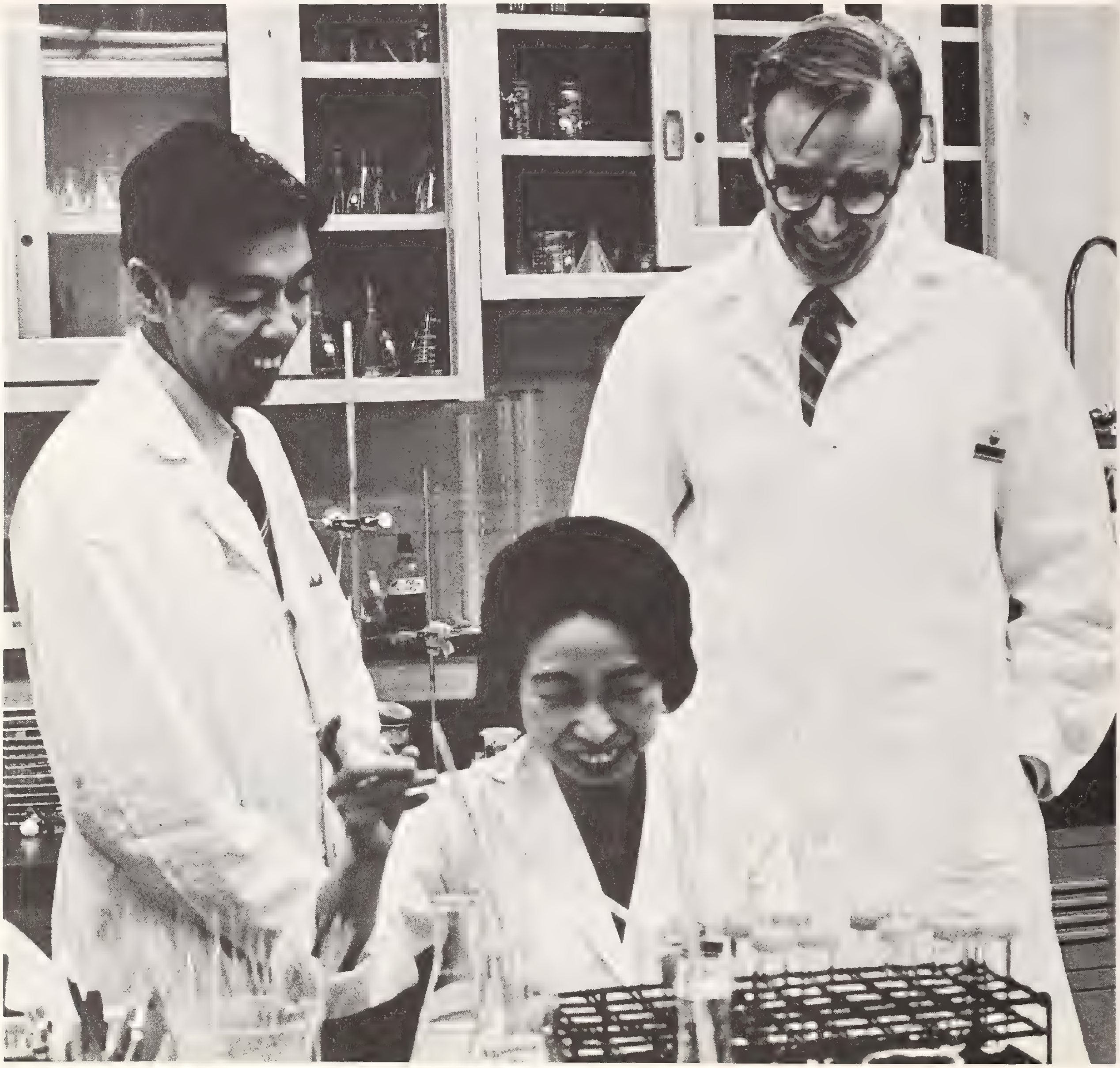
St. Louis, MO	Washington University Medical School, Dr. Charles W. Parker, Director

[See INTRODUCTION on Page Two of This Portfolio]



ANN ARBOR, MI--Kenneth P. Mathews, M.D., head of Asthma and Allergic Disease Center at the University of Michigan, administers a nasal airway resistance measuring device to patient. The device was designed by William R. Solomon, M.D., and James A. McLean, M.D., at Michigan. The mask-like instrument contains sensors which measure pressure and air flow at the entrance to the nose and at the back of the throat. The drop in pressure from the nose to the back of the throat, following administration of an allergen, indicates nasal airway resistance. Through use of an instrument known as an oscilloscope, scientists can quantitatively measure and record this resistance. Studies at Michigan focus on the measurement of airway resistance following manipulation of immunologic, pharmacologic, and irritative factors. The Asthma and Allergic Disease Center is supported by the National Institute of Allergy and Infectious Diseases. (NIH Photo #A-1)



BALTIMORE, MD--Kimishige Ishizaka, M.D. (left), and his wife Teruko Ishizaka, M.D., have done fundamental research into the cause and mechanisms of allergic reactions. Working as a team, they have investigated many aspects of the antibodies (ordinarily protective substances in the blood) which, in the case of allergy, cause tissue damage and produce disease. The discovery by the Ishizakas of a new class of antibodies (IgE) involved in the allergic disease process has opened a new era of research into hypersensitivity reactions and has provided leads for the development of better ways to diagnose and treat allergic patients. The Ishizakas are shown with Philip S. Norman, M.D. (right), who heads the Asthma and Allergic Disease Center at the Johns Hopkins University. The Center is supported by the National Institute of Allergy and Infectious Diseases. (NIH Photo #A-2)

BALTIMORE, MD--Lars Belin, M.D., from Sweden, a visiting scientist at Johns Hopkins' Asthma and Allergic Disease Center, and his assistant, Karen Wheat, are engaged in research on extracts of allergy-producing substances, such as ragweed. Chemical treatment of these extracts weakens them to the extent that they may safely be used in desensitization procedures in the large doses sometimes required for satisfactory results. The Center is supported by NIH's National Institute of Allergy and Infectious Diseases. (NIH Photo #A-3)

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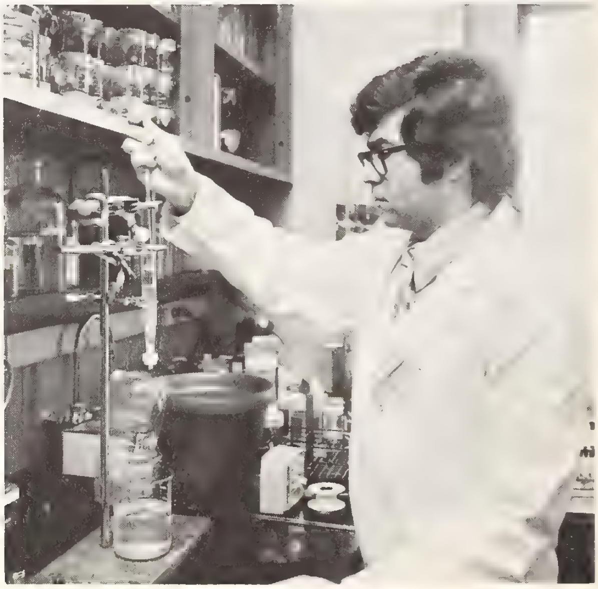


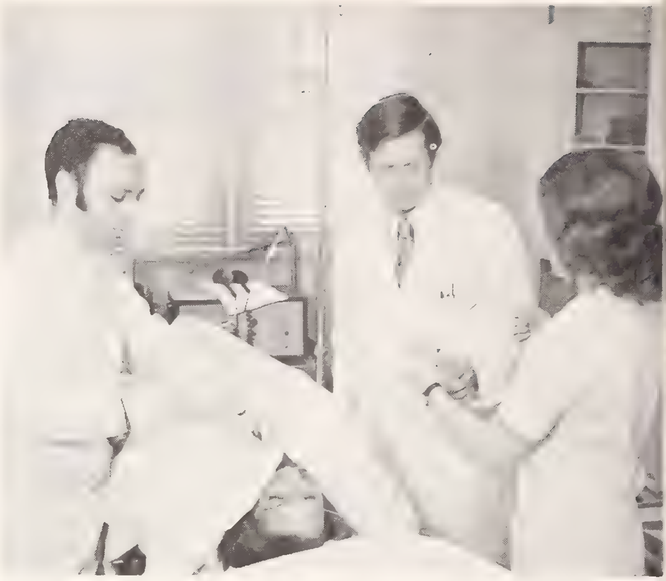
BETHESDA, MD--Studies at the Asthma and Allergic Disease Center at the NIH Clinical Center are focusing on the biochemical pathways leading to the release of mediators such as bradykinin and histamine which produce the symptoms of allergy. These studies, according to Center Director, Allen P. Kaplan, M.D., will be applied to patients with various types of urticaria and angioedema. In the latter, the reaction takes the form of swelling of both internal and external areas of the body. On these pages, Dr. Kaplan is shown (1) assaying

④

③

clotting enzymes with laboratory assistant Charles Tolbert (left), (2) purifying a kinin-generating enzyme, and (3) and (4) conducting a bioassay of bradykinin on specialized equipment using guinea pig intestine. In Photo (3) Dr. Kaplan (left) is assisted by Louis W. Heck, M.D. This Asthma and Allergic Disease Center is an intramural program of the National Institute of Allergy and Infectious Diseases. **(NIH Photos #A-4, #A-5, #A-6, and #A-7)**

Madison WI



La Jolla CA

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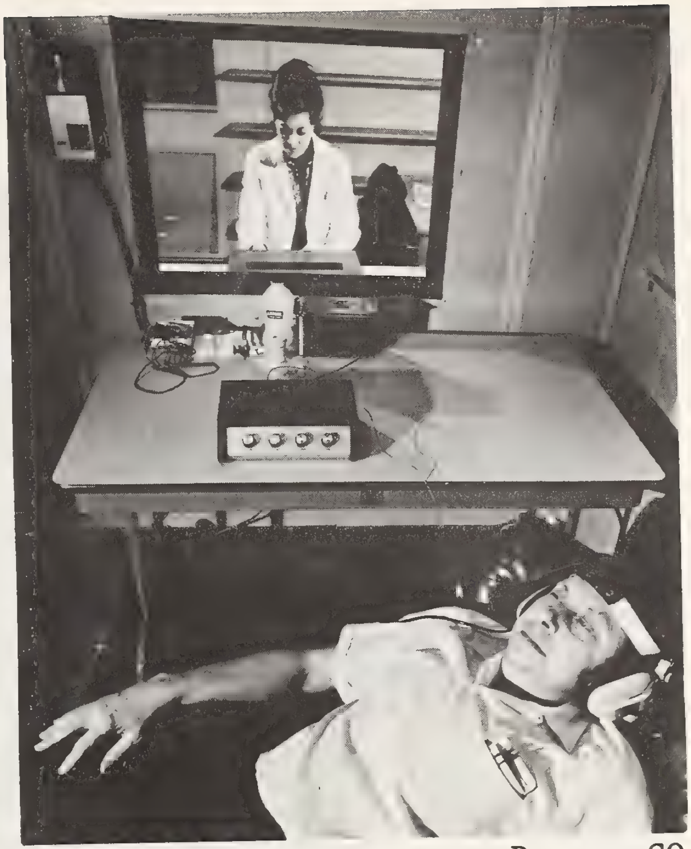
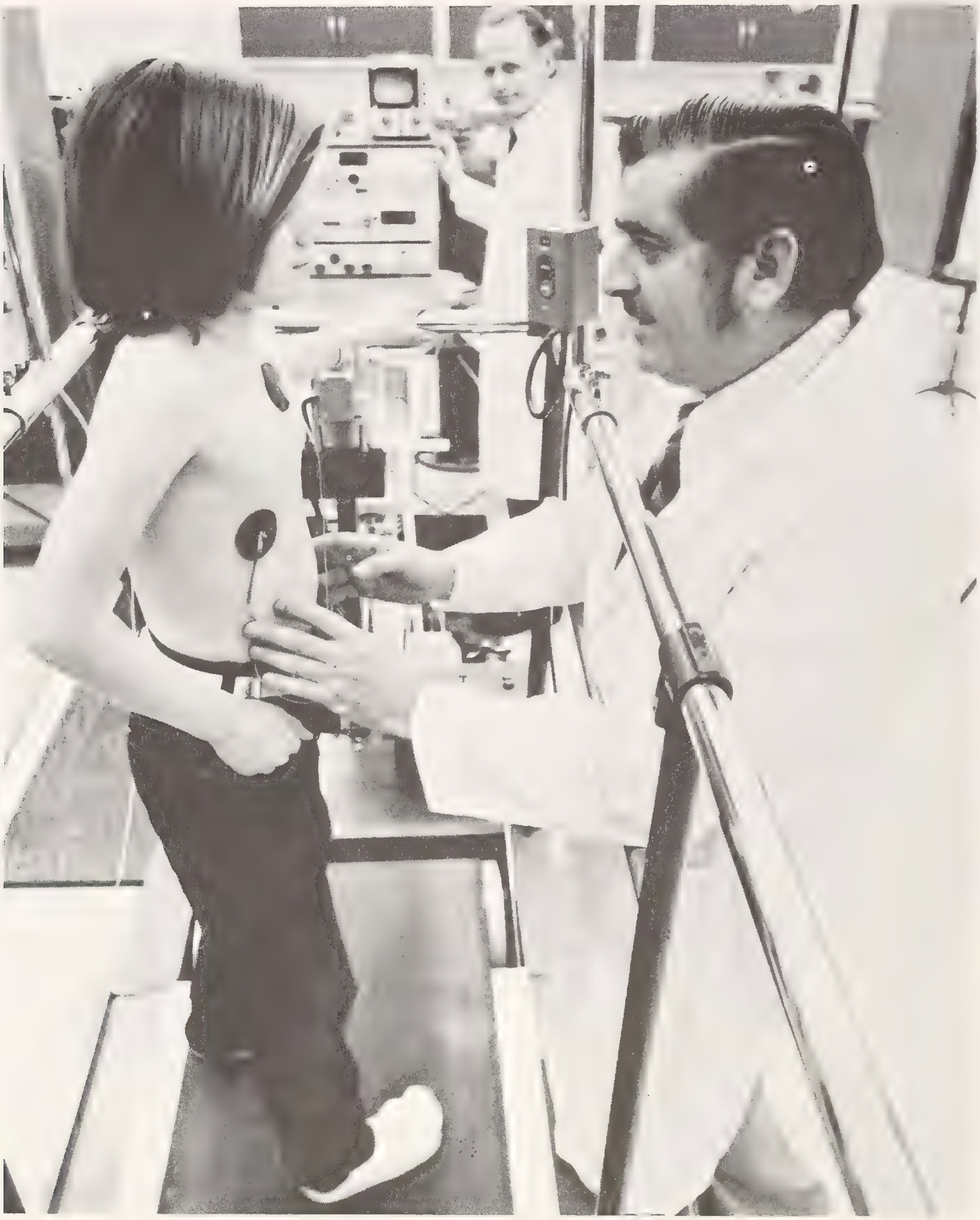


Denver CO

Madison WI

BOSTON, MA--K. Frank Austen, M.D. ***(left)****, director of Asthma and Allergic Disease Center at Robert B. Brigham Hospital, and Shaun Ruddy, M.D., clarify tests on chemical mediators responsible for allergic phenomena. In an allergic individual, after an antigen-antibody reaction takes place, it is followed by a series of biochemical events that take place on a cell or in the body fluid. Regardless of where they take place, these biochemical processes release small molecules called chemical mediators. The chemical mediators of the allergic reaction are a heterogenous group of chemicals--amines, peptides, and acidic lipids. Some of them (such as the amines) exist in the cells in their final form and are simply secreted. Others (such as the kinins and SRS-A) must be formed and released. But despite diverse chemical structure, they all contract smooth muscle and increase vascular permeability, thus contributing to the symptoms of allergic disorders. The Center is supported by the NIH's National Institute of Allergy and Infectious Diseases.* **(NIH Photo #A-8)**

BUFFALO, NY--Anthony Yurchak, M.D. (left) injects a rabbit with bee venom, assisted by John Wypych, M.D. Studies in animals are preliminary to tests in humans of various components of insect venom. This research is directed toward the development of more specific and effective methods of protecting patients against the hazards of insect stings. Studies at the Asthma and Allergic Disease Center of the State University of New York at Buffalo are supported by NIH's National Institute of Allergy and Infectious Diseases. (NIH Photo #A-9)



DENVER, CO--At the Children's Asthma Research Institute and Hospital (CARIH), Hyman Chai, M.D. (foreground) and Gerd J. A. Cropp, M.D., Ph.D., administer exercise tolerance test to an asthmatic patient. On the same day, the child provides the laboratory with blood sample for the study of enzyme activity in the leukocytes. Since scientists cannot directly determine enzyme activity in the lung, they are hoping that "simultaneous" study of pulmonary function and blood enzymes may give a clue to the biochemical status of a patient's lungs on a particular day. Preliminary evidence from these studies indicates that exercise-induced asthma may be related to abnormal enzyme activity. The Asthma and Allergic Disease Center at CARIH is supported by the National Institute of Allergy and Infectious Diseases. (NIH Photo #A-10)

DENVER, CO--Scientists at the Asthma and Allergic Disease Center of the National Jewish Hospital and Research Center study exercise-induced asthma. The treadmill is electronically controlled by the patient's heartbeat. The National Institute of Allergy and Infectious Diseases supports the Asthma and Allergic Disease Center. Major studies include a multidisciplinary approach to understanding and treating intractable asthma. (NIH Photo #A-11)

LA JOLLA, CA--A model patient at Scripps Clinic and Research Foundation Asthma and Allergic Disease Center undergoes pulmonary challenge. A baseline spirometer measures volume and flow rate of expiration in patient given aspirin or other allergen challenge. The Asthma and Allergic Disease Center is supported by the National Institutes of Health, through the National Institute of Allergy and Infectious Diseases. Major studies include aspirin sensitivity and asthma.
(NIH Photo #A-12)

MADISON, WI--Charles Reed, M.D., director of the Asthma and Allergic Disease Center at the University of Wisconsin, characterizes antibodies found in blood serum samples from asthma patients and normal children participating in the Center's study of infectious asthma. The Asthma and Allergic Disease Center is supported by NIH's National Institute of Allergy and Infectious Diseases. (NIH Photo #A-13)

A STUDY IN MADISON: INFECTIONS AND ASTHMA

Since infections account for half of the attacks of asthma and most of the serious ones (especially in children), attempts to answer several categories of questions were made by the Asthma and Allergic Disease Center at the University of Wisconsin, Madison. The questions considered were:

> Which of 100 or more viruses cause the attacks? Does the same virus cause the attacks over and over? What is the role of bacterial infections in respiratory infections? Are they associated with the attacks?
>
> What is the difference between children who get asthma with colds and those who do not? Do they have more infections by different agents? Do they have different immune response? Are they allergic to agents that cause infections?
>
> What is the mechanism of the attack? How does it happen?

Fifteen Madison families were selected to help answer the questions. Each family had one child who had suffered at least four asthma attacks associated with respiratory infections the winter before the study began. Another child in each family was healthy. All children ranged in age between five and 12, and were patients of John Ouellette, M.D., and Marcus Cohen, M.D., of the allergy section and practicing physicians in the Madison community.

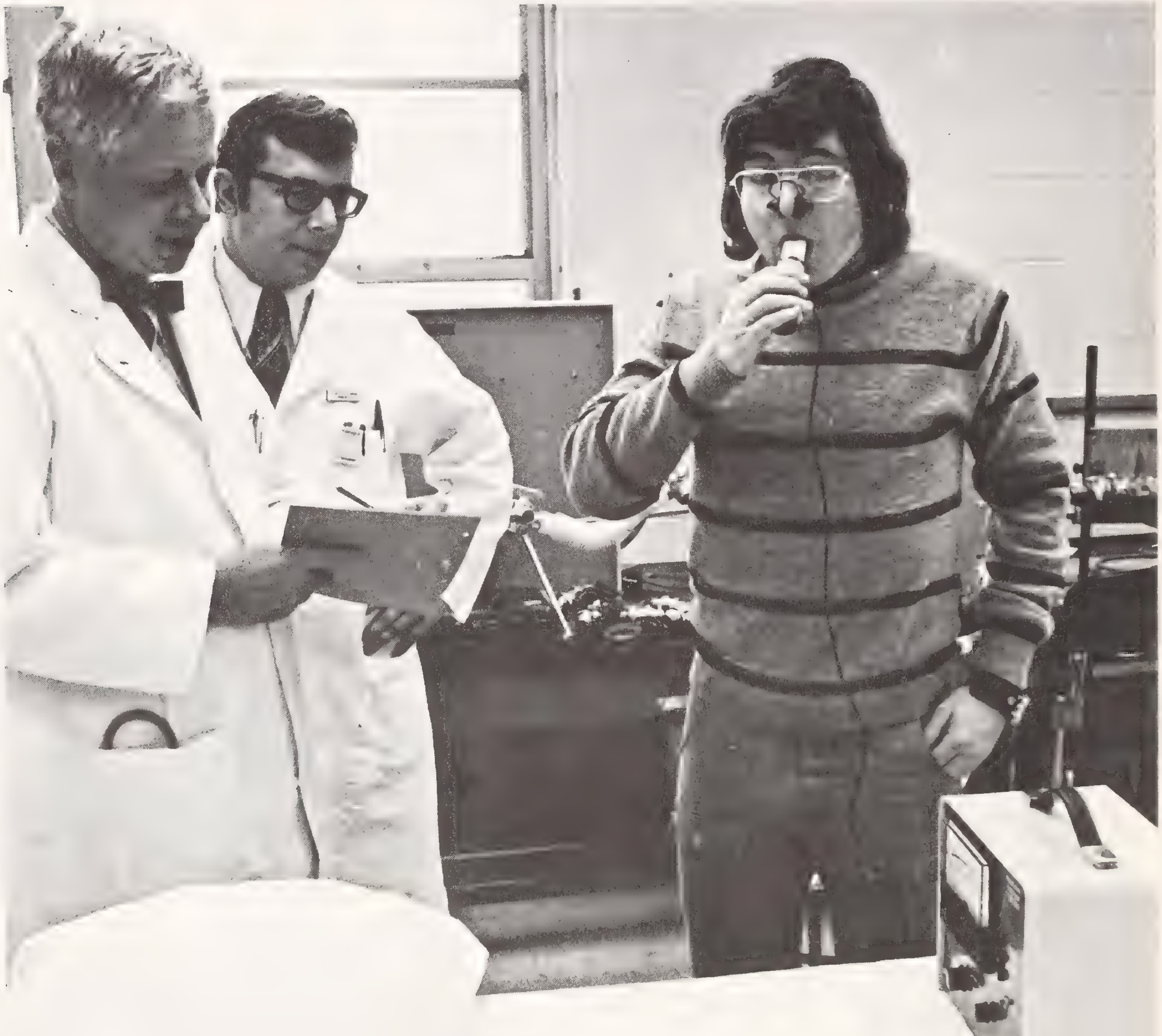
Nurse specialist Ann Perry visited each of the fifteen families twice weekly beginning in October of 1971 through May of 1972. Throat swabs were taken during each visit and cultured for viruses, mycoplasma, and bacteria. The culture was also taken each time a child was ill. Blood samples were taken at the beginning of the study and every six weeks to measure antibody to virus. Samples of nasal secretions were taken every six weeks as well, also for antibody studies. A series of 12-hour urine collections were taken for catachalomines. Each mother kept a daily record of symptoms.

It was found that the infections that cause the asthma attacks are the common respiratory viruses, especially the common cold virus (rhinovirus). Several of these rhinoviruses were isolated. Bacteria turned up only occasionally. The second most common virus was found to be the influenza virus.

It was also found there was no difference between the sick and healthy child in the number of times the researchers were able to isolate an infectious agent and in the kinds of agents isolated. The infections also lasted the same number of days in sick and healthy children.

The samples of nasal secretions and blood are still being analyzed. It has not yet been determined if the sick children are allergic to the viruses. Scientists are beginning to study the mechanism of the attack.

MADISON, WI--Nurse Ann Perry takes throat cultures from an asthmatic child and his normal sibling during a regular semi-weekly visit in the home of one of the 15 families participating in the infectious asthma study of the Asthma and Allergic Disease Center at the University of Wisconsin. The National Institute of Allergy and Infectious Diseases supports the Center. (NIH Photo #A-14)



ST. LOUIS, MO--Charles W. Parker, M.D. (left), and Dixie E. Snider, M.D., conduct a pulmonary function test on a patient at the Washington University School of Medicine Asthma and Allergic Disease Center. Major studies at the Center include bronchial asthma and the failure of some patients to respond to drugs such as adrenaline. The scientists have obtained some evidence that in patients with severe asthma there is a change in the response of cyclic AMP--an intracellular messenger for a variety of hormones. This finding may help explain both development of the disease and the difficulty physicians experience in treating it. The Center is funded by the National Institute of Allergy and Infectious Diseases. (NIH Photo #A-15)

NEWS&FEATURES FROM NIH

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE ■ Public Health Service ■ National Institutes of Health ■ Office of Information ■ Bethesda, Maryland 20014

April 25, 1973

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NEWS & FEATURES From NIH April 25, 1973

Research Advances

In Children...

NEW FINGERPRICK BLOOD TEST DIAGNOSES LEAD POISONING

A new fingerprick blood test provides a simple, reliable, and rapid technique for mass analysis of lead poisoning in children.

The new test, developed by Dr. Douglas G. Mitchell and associates Kenneth M. Aldous and Gordon B. Patrie of the New York State Department of Health, requires only a few drops of blood from the child's finger. It utilizes sophisticated measuring equipment and a computer to analyze lead levels in the blood with greater speed, more reliability, and lower laboratory costs than previous methods. This research was supported by a General Research Support Grant from the NIH Division of Research Resources.

Approximately 380,000 children between the ages of one and five are exposed to lead poisoning related to substandard housing in New York State. According to Dr. Mitchell, until recently, the only accepted screening procedure for this disease was the collection by venipuncture of a sample of whole blood and the determination of the total lead level. However, this sampling procedure is impractical with children up to two years old because of the difficulty in finding the vein. Also, Dr. Mitchell explains that venipuncture procedures meet with strong psychological resistance from parents as well as from their children.

In their initial attempts to analyze fingerprick blood samples for lead poisoning, Dr. Mitchell and associates found their samples contaminated by lead in sweat, air particulates, and skin dirt. Rigorous scrubbing

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procedures prevented sample contamination at the source, but these procedures were time-consuming and difficult to enforce.

In the new test, the investigators avoid lead contamination by spraying the skin with a layer of collodion. When this dries and forms a film, they can prick the skin through the layer, thus avoiding any contact between the blood sample and the surface of the skin. The blood wells up onto the film and is removed by a tiny capillary tube--called a "magic straw" for the children.

To evaluate their new sampling procedure, the investigators compared the results of lead analysis of both venipuncture and fingerprick samples drawn from 24 children, age one through seven years, and a group of 15 adults. They used three fingerprick sampling procedures with the adults: scrubbing, dropping collodion onto the skin with an eyedropper, and spraying collodion onto the skin.

Results of these studies showed that while both collodion procedures give reliable results, the spray procedure is preferred because the coating is much easier and quicker to apply and because there is less risk of contamination of the collodion solution.

One important benefit of the new test is that it does not require the use of a syringe or a large blood sample--two factors which have kept some parents from seeking lead testing for their children. Another advantage is the speed with which the analysis can be performed. The whole process, from vaporization of the sample to printed results, takes 10 seconds. The procedure provides faster service for mass testing and may even double the

(more)

daily output of a testing laboratory.

This new test for lead poisoning has been field tested and is now operational throughout New York State. According to preliminary results, approximately 10 percent of the blood samples analyzed to date contain dangerous lead levels.

Technician Frank J. Ryan, Albany, New York, sprays collodion on Jeffrey Weinbloom's finger before taking a few drops of blood for lead analysis. This new fingerprick blood test for lead poisoning was developed by investigators at the New York State Department of Health with support from the NIH Division of Research Resources. (NIH Photo #1041)

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Research Advances

ANIMAL MODEL CONFIRMS HUMAN GONORRHEA STUDIES

One of the major roadblocks in gonorrhea research is that natural gonorrhea infections occur only in humans. An understanding of the disease is dependent, therefore, on animal models in which the gonococcus organisms can be experimentally grown, tested, and studied.

Scientists may be a step closer to finding an ideal animal model as a result of research carried out by Thomas M. Buchanan, M.D., and Emil C. Gotschlich, M.D., at Rockefeller University, New York City. In a study supported by the National Institute of Allergy and Infectious Diseases (NIAID), the investigators found that gonococcus types 1 and 2 caused infection in the chick embryo more often than types 3 and 4. This is analogous to the situation in humans and is the first time that scientists have confirmed in an animal model the correlation that exists in human beings between colony type of the gonococcus organism and its ability to cause infection.

The chick embryo has been used by scientists for some time to grow the gonococcus organism. The Rockefeller study and others indicated that gonococci usually produce an infection of the chick embryo chorioallantoic membrane that is similar to gonococcal urethritis and cervicitis in humans. In both instances, the infection is local and the frequency of bacteremia is low. Although other animal models--such as the rabbit--are available, the chick embryo offers the advantage of being inexpensive and convenient to use.

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Gonorrhea (Cont'd)

In this study, Drs. Buchanan and Gotschlich inoculated a total of 256 10-day old embryonated eggs with the four different colony types of two strains of *Neisseria gonorrhoeae*--F62 and 2868. When they inoculated less than 1,000 gonococci into the chick embryos, no infection of the chorio-allantoic fluid occurred regardless of the strain or colony types. However, when the investigators inoculated between 1,000 and 200,000 organisms of strain 2868, they found that types 1 and 2 gonococci produced infection in 69% of the embryos, compared to only 11% of infections when types 3 or 4 were used. The results for the F62 strain were almost identical.

The demonstration that gonococcal colony types 1 and 2 are more infective than types 3 and 4 for both man and the chick embryo suggests some fundamental differences among colony types. Recently, other scientists supported by NIAID have demonstrated that filamentous structures--known as pili--are present on types 1 and 2 but are absent from types 3 and 4. Whether these pili play a pathogenic role or are merely markers of other virulence factors has not yet been determined.

The grantees reported their results in the January 1973 issue of the *Journal of Experimental Medicine*.

#

Research Advances

NIDR SCIENTISTS INVESTIGATE DEFENSES AGAINST VIRUSES

A team of virologists at the National Institute of Dental Research has thrown new light on the way the fever blister virus (herpes simplex) avoids antibodies, the first line of defense against infections, while invading uninfected neighboring cells. Antibodies are proteins manufactured by the body in response to exposure to specific foreign substances.

The scientists, working under Abner L. Notkins, M.D., also have shown that certain white blood cells can form a second line of defense against the herpes simplex virus even when the viral particles are enclosed and protected within tissue cells. Perhaps, if enough of these white blood cells can be summoned from the vessels into the infected area and activated against a virus, fever blisters and other recurring viral infections can more readily be cured.

Type 1 of the herpes virus is not only the cause of fever blisters (cold sores), but also under certain circumstances can cause brain damage and death. The virus frequently invades the skin following burns or eczema and attacks the eyes of approximately 500,000 people in the United States, often resulting in blindness. Type 2 of this virus attacks the urogenital system of an estimated 100,000 persons a year, and might be linked to cervical cancer.

Dr. Notkins explains that viruses can grow and multiply only in cells, not in the blood stream. Usually they grow at the expense of the life of a cell: when they mature the cell wall breaks and the released viral particles

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spread between neighboring cells and infect some of them. At this stage of release, antibody and complement together inactivate most viral particles. (Complement is a group of at least nine serum proteins which operate in series to control many immune reactions.)

Dr. Notkins points out that herpes virus is notorious for surviving even when its victims have ample antibody to neutralize the virus and normal levels of complement to assist in the process. Antibody and complement slow but do not stop the spread of herpes because the virus can also pass directly from cell to cell through "intercellular bridges" without exposure to antibody.

Earlier studies showed that viral antigens appear on the surface of cells a few hours after infection, and that antibody and complement attack and destroy those cells which have developed viral antigens. But, in the present study, Dr. Notkins' group found that such cell destruction occurs too late to stop the spread of infection. The tiny virus always escapes through the "bridges" just one step ahead of the proteins.

The investigators also studied certain leukocytes or white blood cells (chiefly macrophages) which, if sufficiently activated, will migrate from blood vessels into tissue and there remove unwanted dead cells, bacteria, viral particles, antigen-coated cells, and other products damaging to the body. The scientists reasoned that if a large number of activated leukocytes can kill infected tissue cells, perhaps a smaller number might be less deadly but still sufficiently toxic either to arrest the metabolic system of the infected cell enough to prevent the virus from using it to multiply, or to

(more)

prevent the formation of bridges between cells. Either or both reactions would control the infection.

After the scientists tested various concentrations of activated rabbit leukocytes on their cultures of herpes-infected rabbit kidney cells, they found that a limited number of the white cells do allow the kidney cells to survive with no evidence of viral spread. But three days after removing the leukocytes, the virus again multiplied and spread. Obviously the white cells alone temporarily checked, but did not cure, the infection.

Next, the virologists exposed cultures of infected cells to all three components: antibody, complement, and leukocytes. In the absence of leukocytes, antibody and complement did not stop the spread of infection. However, when the scientists added antibody and complement after the leukocytes had time to inhibit the cultures but before bridges could reform, and then removed the white cells, the infection was cured.

These experiments suggest to Dr. Notkins' team that protection against herpes and probably other recurrent viruses requires an ability to make antibody, a complete and active complement system, and the ability to activate and attract leukocytes quickly to sites of infection. Deficiencies in any one of these immune responses must be understood and counteracted if viruses are to be controlled.

This research was reported by Donald L. Lodmell, Ph.D., Akira Niwa, M.D., D.M.S., Kozabouro Hayashi, M.D., and Dr. Notkins in the March issue of the *Journal of Experimental Medicine*.

#

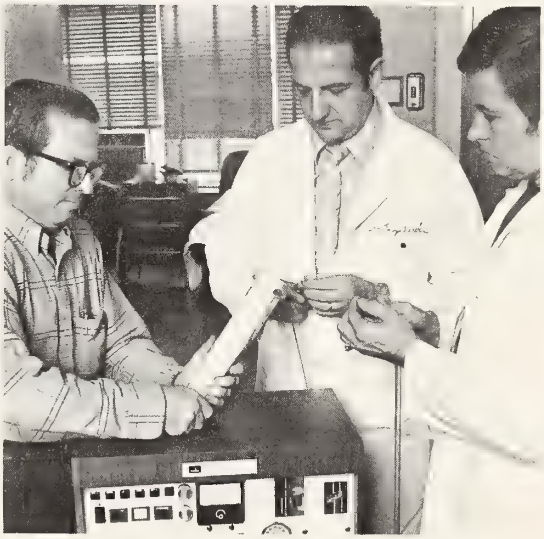
Photo-Feature

NEW DISPOSABLE ARTIFICIAL KIDNEY PERFORMS DIALYSIS 30% FASTER

Researchers at the University of Chicago and the Argonne National Laboratory have developed a new compact and disposable artificial kidney (dialyzer) that is 30% faster than any other artificial kidney now in use. This new dialyzer is small enough to be operated without a blood pump, utilizing the patient's own blood pressure instead. It has the potential for economical daily home use and allows the patient to eat, move around the room, and perform other chores while undergoing dialysis.

Edmund J. Lewis, M.D., director of the Hemodialysis Unit at the University of Chicago and a grantee of the National Institute of Allergy and Infectious Diseases, has directed over 70 successful clinical tests on the new artificial kidney since last October. Dr. Lewis is associate professor and chief of the Section of Nephrology of the Department of Medicine in the University's Division of the Biological Sciences and The Pritzker School of Medicine.

The new device is the invention of Finley Markley, formerly an associate physicist at the Argonne National Laboratory, whose research was funded by the Atomic Energy Commission.



Finley Markley (left), inventor of the new artificial kidney, examines the device with Edmund J. Lewis, M.D. (center), grantee of National Institute of Allergy and Infectious Diseases. Assisting is Evalds Butners (right), chief technologist in the Hemodialysis Unit of the University of Chicago where Dr. Lewis directed over 70 successful clinical tests of the new dialyzer. (NIH Photo #1042)

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Like all kidney dialyzers, the new artificial kidney utilizes cellophane as a membrane material through which waste products in the blood, urea, and creatinine pass into a specially-prepared fluid (dialysate) on the other side of the membrane. In one run during 30 test hemodialyses, the new device removed urea from an average of 146 milliliters (ml.) of blood per minute, while the human kidney's capacity is 75 ml. per minute; and it removed creatinine from 117 ml. per minute in comparison to the normal human kidney rate of 120 ml. per minute. Additionally, the device removed ninety percent of the urea and seventy-three percent of the creatinine, Dr. Lewis reported.

Although it contains 1.2 square meters (sq.m.) of membrane surface, which is larger than other dialyzers (most contain 1 sq.m.), the Argonne dialyzer measures only 2 x 2 x 12 inches. The unit's compactness is due to Markley's discovery of an adhesive capable of bonding cellophane so that it will withstand immersion in water. This permitted the cellophane membranes to be placed in 60 accordion-folded pleats supported by polypropylene mesh, rather than in the less efficient arrangement of cellophane tubes which had been used previously.

The unit, contained in a polycarbonate case, uses less blood to prime than other dialyzers and requires only 30 ml. of blood for operation instead of the 100 to 250 ml. necessary for other dialyzers. It is disposable after use and is expected to cost about $15 when commercially available.

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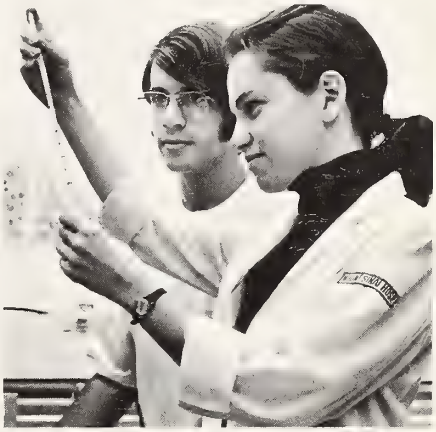
This Photo-Feature was prepared by Thomas H. Flavin, NIH Information Intern.

At Mount Sinai...

Photo Feature

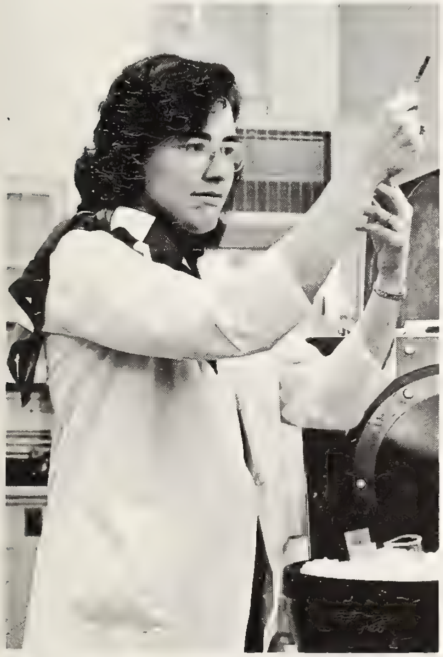
WOMEN RESEARCHERS BATTLE DISEASE

Ruth Abramson, M.D., assistant professor of medicine, Mount Sinai School of Medicine, City University of New York, is studying urate transport in the kidney by means of micropuncture. Dr. Abramson is a grantee of the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD). (NIH Photo #1043)



Terry A. Krulwich, Ph.D., assistant professor of biochemistry at Mount Sinai, is also funded by NIAMDD. Here Dr. Krulwich teaches M.D.-Ph.D. student Mark Sobel how to isolate bacterial mutants which are defective in glucose metabolism. (NIH Photo #1044)

Diana S. Beattie, Ph.D., is researching the synthesis of mitochondrial protein under a grant from the National Institute of Child Health and Human Development. Dr. Beattie, an associate professor of biochemistry at Mount Sinai, is preparing tissue for the centrifuge. (NIH Photo #1045)



Dorothy T. Krieger, M.D., a National Institute of Neurological Diseases and Stroke grantee, is professor of medicine at Mount Sinai. Dr. Krieger's project is tracing the effects of blindness on adrenal periodicity. (NIH Photo #1046)

#

News Feature

At Professional Meeting...

SCIENTISTS DISCUSS DETAILS OF HEXACHLOROPHENE STUDIES

In September 1972, the Food and Drug Administration (FDA) banned the non-prescription sale of hexachlorophene (HCP), the antibacterial agent widely used in hospital nurseries for bathing newborn infants. Previously, the FDA had warned physicians that infants washed with the compound showed detectable amounts of the chemical in their blood and that studies in monkeys indicated that HCP caused a particular type of brain damage--bubbling of the myelin sheath that insulates the nerve fibers in the brain stem.

In February, scientists at the University of Washington School of Medicine in Seattle reported for the first time in public to a professional audience the findings in human infants that lay behind the September decision. The report, by Robert M. Shuman, M.D., Richard W. Leech, M.D., and Ellsworth C. Alvord, Jr., M.D., documents the difficulties the investigators faced in implicating HCP as the cause of damage to brain tissue in infants. Their study is supported by NIH through grants from the National Institute of Neurological Diseases and Stroke and the National Institute of Child Health and Human Development.

HCP is a powerful antibacterial agent. First synthesized in the early 1940's, its use became widespread in the 1950's in the form of soap (containing 3 percent HCP). With its use, the incidence of staphylococcal infections among newborns in hospitals dropped dramatically. Such "hospital staph" infections can sweep through a hospital nursery leaving a trail of life-threatening diseases such as pneumonia, meningitis, and blood poisoning.

About ten years ago, the University of Washington pathologists noticed that some children had died with a particular kind of abnormality of brain

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tissue. "We had no idea what the cause of the damage might be," said Dr. Shuman, "until early last year when we realized that there was a similarity between the bubble-like lesions we saw in our autopsy specimens and those reported in monkeys that had been treated with HCP."

This realization led the scientists to take another look at the medical records of these cases. Because of the grantees' long experience with brain damage in the newborn child, they had a sufficient number of cases in their files of pathological specimens to determine adequately whether sufficient HCP could be absorbed through the skin of the infants to produce the brain damage they saw at autopsy.

The fact that the two major hospitals in the area caring for premature infants differed dramatically in their use of HCP on newborns also helped the investigators in their studies. The nurses at both hospitals kept complete records of actual treatment of the babies.

Children's Orthopedic Hospital diluted the HCP soap 100-fold in water (making HCP content 0.03 percent) and used it only to wash limited areas of the skin. Direct application of undiluted HCP soap was limited to local preparation for a surgical procedure.

The University Hospital, on the other hand, used undiluted HCP soap to wash the entire bodies of the infants. All newborns were washed with HCP soap applied directly to the skin. The soap was rubbed to a lather over the entire body surface. Infants greater than two and one-half pounds were immersed in a basin of water to remove the soap. The soap was removed from smaller infants by dripping water over their bodies with water-soaked cotton balls instead of by immersion.

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Of 250 cases of infant and child deaths under the age of five years that Dr. Shuman and his associates studied, 21 showed the bubbly pattern in the brain tissue that the investigators had originally associated with HCP in monkeys. All but one of these cases had been exposed to undiluted HCP at University Hospital, 18 cases occurred in premature infants weighing under two and one-half pounds at birth, and all but two of the 21 cases had been given three or more total body baths with HCP soap.

Since exposure to the HCP was by a daily bath, a child who received three baths would have survived at least three days, the investigators concluded. Also, since the smaller premature infants frequently are not bathed until their second day of life (because they are generally unstable at birth), Dr. Shuman determined that the infants would need four hospital days to be bathed three times. The investigators found no brain damage associated with HCP in infants weighing less than one and one-half pounds at birth because they did not survive long enough.

The explanation for the sharp drop in the frequency of the lesion in infants weighing more than two and one-half pounds is not clear. It could be related to decreased permeability of the more mature skin, to the more complete rinsing away of HCP by immersion, or to the increased ability of the more mature liver to detoxify absorbed HCP.

The peculiarity of the damage that HCP causes in brain tissues was partly responsible for the many years between the recognition and coding of the lesions and the final establishment of its cause. To a pathologist, the bubbles (or vacuoles) resembled the artifactual damage that may be seen following preparation of the brain specimen for examination under the microscope. Also, unlike

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most other agents that damage the brain, HCP appears to cause only the bubbly changes without any subsequent healing or scarring.

Their studies led the Seattle investigators to make three recommendations about the use of hexachlorophene:

(1) It should not be used in any way on infants of less than 1,400 grams (two and one-half pounds).

(2) It should not be used on individuals of any age with skin defects.

(3) If necessary for control of infection among full-term infants, it should probably be diluted to a level yet to be determined as both effective and safe.

Dr. Shuman and associates reported their findings at the American Association of Pathologists and Bacteriologists meeting in Washington, D.C., February 25, 1973.

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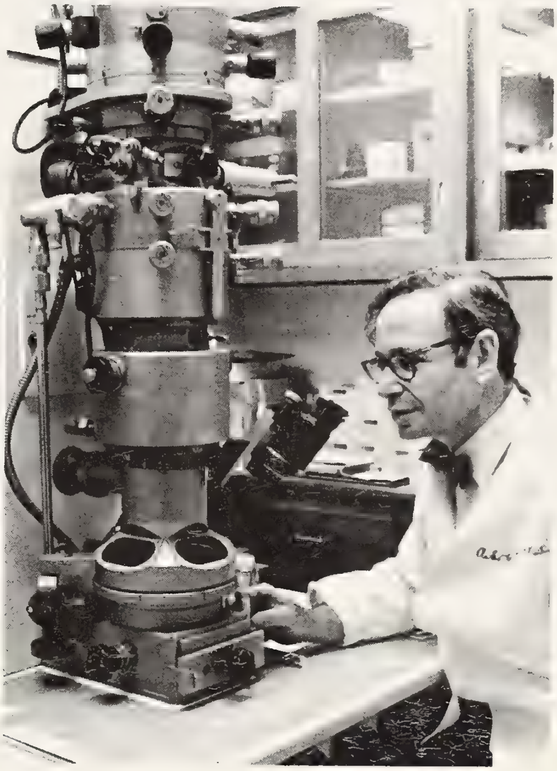
Photo Feature

RESEARCHERS ATTACK AMYLOIDOSIS, STUDY JOINT MEMBRANE DISEASE



Alan S. Cohen, M.D., will head a Boston University Medical Center research team studying amyloid disease (amyloidosis) and various disorders of the joints. The research, at the Evans Memorial Department of Clinical Research, will be supported by a grant of $548,194 from the National Institute of Arthritis, Metabolism, and Digestive Diseases. Amyloidosis, a disorder marked by deposits of an unusual protein called amyloid at various parts in the body, is a severe complicating factor in a wide spectrum of diseases including rheumatoid arthritis, tuberculosis, and diabetes mellitus. Over the past decade, Dr. Cohen's research group in the Medical Center's Arthritis and Connective-Tissue Disease Section has become a world leader in establishing the characteristics of amyloid substance and developing techniques for treatment of amyloidosis. The group will also study the role of the joint membrane. Using tissue culture techniques now often employed in cancer research, they will seek evidence, among other studies, for a possible viral link to diseases of the joints (especially rheumatoid arthritis). (NIH Photo #1047)

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Medical News Tip

CORONARY BY-PASS SURGERY IMPROVES BLOODFLOW TO THE HEART--Surgery to by-pass obstructions in the coronary arteries may produce immediate, often striking improvement in patients with severe pain from heart disease.

In this procedure, segments of vein are removed from the patient's leg. One end of the graft is spliced into the aorta, and the other end is spliced into the diseased coronary artery to improve blood flow. An estimated 20,000 by-pass operations were performed last year.

Since little is known about the long-term effectiveness of the procedure, the National Heart and Lung Institute (NHLI) is undertaking controlled studies to evaluate the long-term effectiveness of coronary by-pass for improving the blood supply to blood-deprived (ischemic) areas of the heart muscle and for relieving angina pectoris and other clinical manifestations of coronary artery disease. The Institute is also seeking to establish criteria for determining which patients are most likely to derive lasting benefits from the operation.

For additional information about coronary by-pass surgery, contact: NHLI Information Office, Landow Building, Room C-918, Bethesda, Maryland 20014, Phone (301) 496-4236.

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New Publications:
Cataract: NEI Focus on Research

Nearly 5,000 people in the United States will lose their sight this year from cataract. However, permanent blindness from cataract is usually needless.

To explain this disease and its treatment, the National Eye Institute (NEI) has issued *Cataract: NEI Focus on Research.* According to this booklet, a cataract is a cloudiness in the lens of the eye which interferes with vision.

While the cause of a cataract cannot usually be determined, cataract extraction is one of the most successful operations performed today. From 90 to 95 percent of all patients undergoing cataract surgery enjoy restoration of sight.

Cataract: NEI Focus on Research discusses the causes of cataract, symptoms, treatment, current and experimental surgical methods, adjustments after surgery, and patient resistance to surgery. The booklet also describes NEI intramural and extramural cataract research.

Science writers can obtain a free copy of this publication from: NEI Information Office, Bldg. 31, Room 6A-27, NIH, Bethesda, MD 20014, Phone (301) 496-5248.

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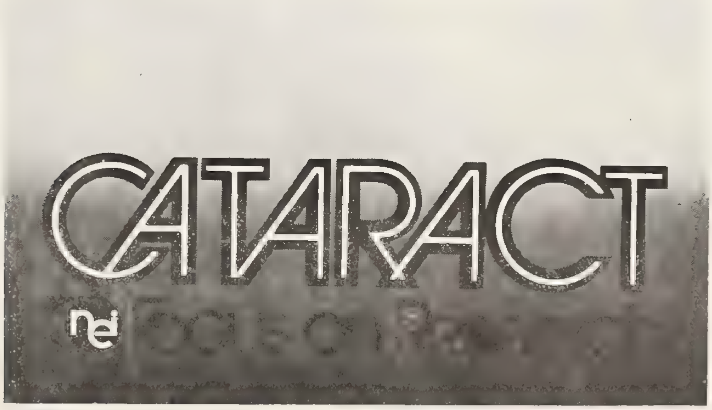

New Publications (Cont'd)

Variations and Connections of the Human Thalamus

A two volume atlas of the human thalamus by John M. Van Buren, M.D., Ph.D. and Rosemary C. Borke, has recently been published by Springer-Verlag, New York.

Dr. Van Buren is Chief of the Surgical Neurology Branch and Acting Clinical Director of the National Institute of Neurological Diseases and Stroke (NINDS). Miss Borke is a biologist in the Branch.

The thalamus, a mass of gray matter located at the junction between the cerebral hemispheres and the brain stem, serves a variety of functions related to modulating sensorimotor activities and higher intellectual effort.

The first volume of this atlas, "The Nuclei and Cerebral Connections of the Human Thalamus," evaluates the anatomy and cell structure of the thalamus. Areas which are distinguished by characteristic cell structure are further defined by their specific connections with the cerebral cortex and subcortical structures.

The second volume, "Variations of the Human Diencephalon," provides a three-plane atlas of the brain for the stereotaxic surgeon. In addition, variations of the standard X-ray surgical landmarks of the deep nuclei of the cerebrum, especially the thalamic nuclei, were studied utilizing standard X-ray surgical landmarks. This unique study serves as a practical "anatomical control" to evaluate the results of the stimulation and coagulation of deep structures employed in the stereotaxic surgical treatment of diseases of the central nervous system in man.

For additional information about the atlas, contact the NINDS Information Office, Bldg. 31, Room 8A-03, NIH, Bethesda, MD 20014, Phone (301) 496-5751.

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News Releases Issued

TISSUE MATCHING--The usefulness of tissue matching in kidney transplants between unrelated donors and recipients will be evaluated by scientists working under contracts from the National Institute of Allergy and Infectious Diseases (NIAID). The nation-wide study, which is expected to extend over a two-year period, will seek to provide answers to critical questions being raised in the rapidly expanding field of kidney transplantation. Six clinical groups will cooperate in the project: the Cleveland Clinic, Cleveland, Ohio; the University of Utah Medical Center, Salt Lake City; the University of Illinois College of Medicine, Chicago; the University of Rochester, Rochester, New York; the University of Texas Medical School, Dallas; and the University of Minnesota Medical School, Minneapolis. The University of North Carolina School of Public Health, Chapel Hill, will serve as a statistics and data management center for the study.

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May 10, 1973

SPECIAL SUPPLEMENT:
NIH Portfolio on the Pharmacology-Toxicology Program

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NEWS & FEATURES From NIH May 10, 1973

Research Advances

PROSTAGLANDINS MAY EXPLAIN BONE LOSS IN PERIODONTAL DISEASE

Scientists may have found an explanation for the bone loss occurring in periodontal disease as well as discovered a possible means of controlling the destruction.

Jo Max Goodson, D.D.S., Ph.D., of the University of California School of Dentistry in San Francisco, reports that in periodontal disease, gingival tissues have ten times the normal levels of a prostaglandin. Prostaglandins are hormone-like chemicals of the body that can increase inflammation and cause bone to resorb or dissolve. Prostaglandins are also involved in such functions as induction of labor.

Bone loss in periodontal disease is usually irreparable. Eventually, the bone loss reaches the point where teeth loosen because there is insufficient bone to support them. Consequently, this disease of the tooth-supporting tissues is the major cause of tooth loss in adults. In this country alone, periodontal disease has left more than 22 million people with no natural teeth. Should drugs which inhibit prostaglandin production prove effective in controlling bone loss, then natural teeth could be retained throughout life.

According to Dr. Goodson, "Our finding that prostaglandin concentrations are so much higher in diseased gingiva than in healthy tissue implicates these chemicals in the bone loss of periodontal disease." Dr. Goodson's research on the role of prostaglandins in periodontal disease is funded by the National Institute of Dental Research and the California Dental Association.

(more)

Periodontal Disease (Cont'd)

Because vitamin E inhibits synthesis of prostaglandins and is generally well tolerated, Dr. Goodson gave 14 periodontal patients a daily dose of 800 milligrams of the vitamin in the hope of reducing inflammation and bone loss characteristic of the disease. The vitamin E trial was funded by the University of California. The patients were instructed to bite the capsule and to swish its contents in their mouths before swallowing. Thus, the vitamin could exert local as well as systemic effects. Another group of patients received placebos.

After 21 days, Dr. Goodson found that the vitamin reduced inflammation as measured by the fluid that flows at the margin between the gingiva and the teeth. In periodontal disease, the gingiva is inflamed. As a result, flow increases.

Although vitamin E has many diverse effects, Dr. Goodson thinks it may have helped the patients by decreasing prostaglandins synthesis and thereby reducing inflammation. Further studies are needed to ascertain whether or not specific drugs can reduce prostaglandin levels in the gums and actually control bone loss.

Last year, Dr. Goodson isolated prostaglandins from diseased human gingiva and showed that the hormone-like substances can induce bone resorption in living animals and in bone growing in culture. The levels he has found in diseased human gingiva are high enough to cause severe bone deterioration in culture.

Dr. Goodson reported his findings at the International Association for Dental Research meeting in Washington, D.C., April 14, 1973.

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Research Advances

STUDY LINKS GENES CONTROLLING HAYFEVER AND HL-A ANTIGENS

Physicians have observed for some time that allergies tend to "run in families"--that is, they are inherited in some way. Now, scientists have strong evidence that the genes controlling expression of some allergies and the expression of the HL-A antigens--those antigens important in tissue typing for transplants--are linked together closely on the same chromosome in man.

This evidence was found by David G. Marsh, Ph.D., and his colleagues at the Johns Hopkins University School of Medicine in Baltimore, Maryland, and Lawrence Goodfriend, Ph.D., at the Royal Victoria Hospital in Montreal, Canada. Dr. Marsh's studies were supported by the National Institute of Allergy and Infectious Diseases and the National Institute of General Medical Sciences.

The scientists made their discoveries while they were studying 105 people with hayfever caused by allergy to ragweed pollen. Their studies focused on people who were sensitive to one of the minor components of the pollen grain, a newly-discovered fraction called Ra5.

According to their findings, only 18 of the people (17%) who were sensitive to the major component of ragweed pollen--antigen E--were sensitive to Ra5. However, a high percentage of these Ra5-sensitive people also had the major histocompatibility antigen, HL-A7, or one of the group of antigens immunologically related to it. People who were insensitive to Ra5 did not show this correlation.

(more)

Genetic control of the immune response is an exciting new area of research that is only now starting to bring in meaningful data. It is now known, for instance, that in certain inbred animal strains, the histocompatibility genes are linked to immune response genes which seem to control responses to a specific antigen. Scientists have long suspected a similar association in man between the HL-A system and a variety of antigens causing human diseases. The present study appears to be the first demonstration in humans of an association between a specific immune response to an antigen and HL-A serotype. Further studies of specific allergic responses in man should aid understanding of the genetic control of immune responsiveness, and, perhaps, lead to correction of immunologic deficiencies.

Drs. Marsh and Goodfriend reported this study in the February 16, 1973 issue of *Science*.

#

Research Advances

INTERFERON MAY HELP PREVENT COMMON COLD AND INFLUENZA

Colds caused by one of the rhinoviruses have been prevented in volunteers by the administration of a nasal spray of interferon--a naturally occurring antiviral substance. Although the results of similar experiments using influenza B virus were not encouraging, the dose of interferon used in these latter studies was probably too small, according to Dr. Thomas C. Merigan.

Dr. Merigan, an National Institute of Allergy and Infectious Diseases grantee at Stanford University, cooperated with investigators at the Medical Research Council's Common Cold Unit, Harvard Hospital, Salisbury, Wiltshire, England in both *in vitro* and *in vivo* studies of interferon prepared outside the body.

Scientists have long hoped to make interferon available as an antiviral drug since it is active against most viruses and has no toxicity. Recently, investigators have developed methods whereby human cells, transferred to an artificial medium for growth, can be stimulated to produce large amounts of interferon. It was this type of exogenous interferon that was used in Dr. Merigan's studies.

Dr. Merigan and colleagues first used cell and organ (trachea) cultures to determine the susceptibility of certain respiratory viruses to interferon. Then, they chose influenza virus and rhinovirus 4 for use in the studies involving 54 volunteers.

When the investigators gave interferon prior to influenza challenge, it failed to alter the subsequent incidence or severity of infection. However,

(more)

a more detailed analysis of the clinical course of disease in the volunteers indicated that disease was delayed in three of 11 of the interferon-treated group. This observation was similar to others made in studies of animal infections treated with borderline effective doses of interferon, suggesting that in future studies, interferon should be administered in larger doses and continued after virus challenge.

In experiments with rhinovirus 4, large doses of interferon were given both before and for three days following challenge with the common cold virus. Only one of the interferon-treated volunteers showed any cold symptoms.

The scientists stress that at present, interferon is far from being a practical remedy for the common cold and other respiratory ailments. For example, in the rhinovirus study, it was necessary to give each volunteer the amount of interferon produced by white cells from some 30 to 50 blood transfusions. Dr. Merigan and his co-workers believe, however, that if interferon proves to be clinically applicable, production techniques will be improved, the cost of interferon will decrease, and the method of administration will be simplified.

Dr. Merigan and associates published a report of the studies in the March 17, 1973 issue of *Lancet*.

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Photo Feature

TASTE BUDS GROWN IN TISSUE CULTURE MAY LEAD TO TREATMENT OF DYSAUTONOMIA

Taste buds have for the first time been grown in organ culture where interaction of tissue and nerves can be observed and controlled. Absence of these minute structures of the tongue make it possible to diagnose at birth the Riley-Day syndrome--a serious nerve disorder (dysautonomia)--affecting infants and children. This syndrome is characterized by indifference to pain, inability to shed tears, emotional instability, drooling, excessive sweating, and poor motor control.

Experiments conducted by Albert Farbman, D.M.D., Ph.D., of Northwestern University and supported by the National Institute of Neurological Diseases and Stroke (NINDS), were designed to provide a model system for taste bud development through which scientists can learn why and how the taste bud tissue develops and regenerates under the influence of nerves. It is hoped that such understanding may lead to an intervention which will be able to prevent the development of dysautonomia.

"We are at a very basic level of our research," Dr. Farbman stressed, when he presented his findings at a March 7, 1973 conference of the New York Academy of Sciences, "but we could open a completely unknown field. We know that both the development and the regeneration of taste bud tissue occurs under the influence of nerves. We have simply never understood the nature of the interaction between nerve and tissue."

The experiment was designed to create a model system in which nerves would induce taste bud differentiation and in which the nerve-cell inter-

(more)

action could be easily manipulated. Such a model system could be used effectively for studies on the specific cellular events associated with the induction of taste buds. It is of interest that no taste buds developed on tissue fragments from the tongue of 16 to 18 day rat fetuses in the organ culture if it did not contain nerve ganglia.

It is highly significant that the organ culture system is not limited to the study of cell differentiation in taste buds only, but can also be useful in the study of other systems in which nerve exerts trophic or inductive effects on tissues.

Further study is needed to determine if there is a single inducing substance or molecule released at a critical time associated with the differentiation or whether there are several acting serially. It appears that in these experiments whatever is required for these cells to become taste bud cells is present in the cultures in only marginal quantities--or at least its effect is marginal--because the yield of taste buds is small. Hormones and other substances added to the culture have thus far failed to increase the yield.

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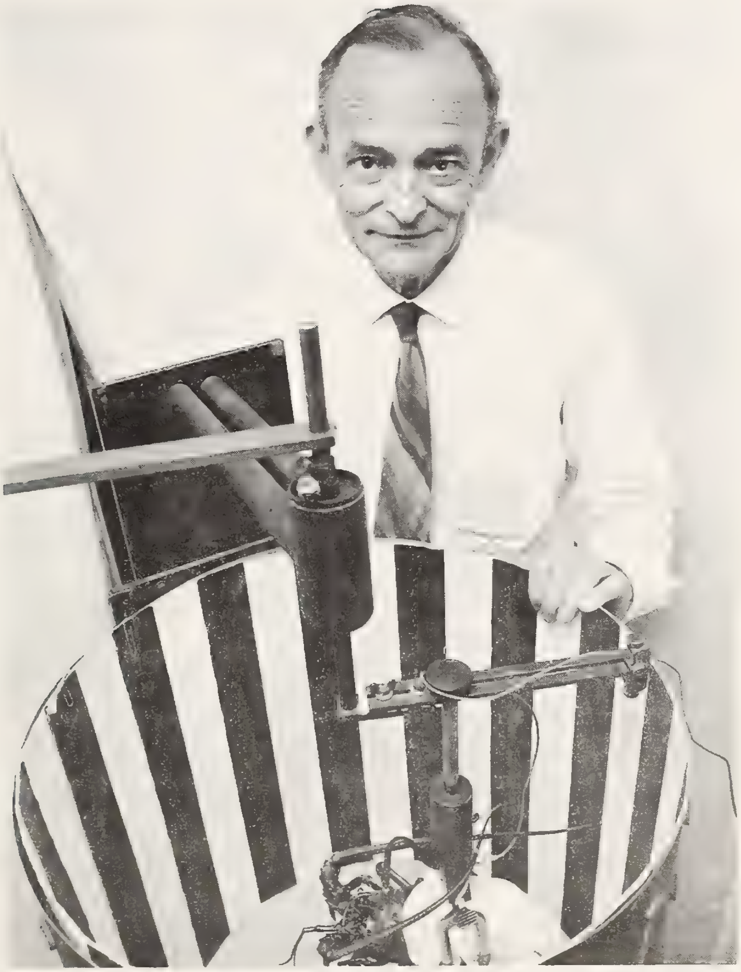
Dr. Albert Farbman, professor of anatomy at Northwestern University Medical School, points out a cell in a taste bud. He is developing taste buds in tissue culture, hoping to provide a model system through which scientists can learn why and how the taste bud tissue develops and regenerates under the influence of nerves. Dr. Farbman's work is supported by NINDS. (NIH Photo #1048)

Photo Feature

CRUSTACEANS USED IN MEMORY STUDY



Cornelis A.G. Wiersma, Ph.D., professor of biology at the California Institute of Technology, is learning how memory works by exploring the recollecting talents of crustaceans. According to Dr. Wiersma, crabs make use of their memories to detect small changes in the position of objects in their vicinity with a precision not possible in humans. While the memories of the young and middle aged crayfish are good, Dr. Wiersma explains that they tend to become hazy with advanced age. The large rock lobster, however, has no memory. Dr. Wiersma and associate Richard L. Hirsh, Ph.D., are using a technique that involves the stalks which carry the crustacean's optic nerves to its periscope eyes. The investigators are tapping an untrained memory that forms within a half second and lasts for about eight minutes. Using this memory, they hope to learn, among other things, how memory controls eye movements. Above, Dr. Wiersma places a lobster in a typical testing apparatus. Funds for this work came from the National Eye Institute. *(NIH Photo #1049)*

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News Feature

IMMUNOTHERAPY OFFERS HOPE FOR SOME LEPROSY PATIENTS

Some leprosy patients may soon be aided by a novel approach to therapy now being evaluated by two groups of scientists supported in part by the National Institute of Allergy and Infectious Diseases (NIAID). Called immunotherapy, the approach involves the use of substances to enhance the immune response in patients with lepromatous leprosy, the most severe form of the disease.

Although leprosy is not considered a major public health problem in the United States, nearly 10 million people worldwide suffer from it. The most severe form of the disease, caused by the microorganism *Mycobacterium leprae*, is lepromatous leprosy.

Lepromatous leprosy goes virtually unchecked in patients with the disease. In these people, cell mediated immunity (delayed hypersensitivity) is often completely missing. They have no skin reaction to the antigens of *M. leprae* (lepromin). Although they have high levels of circulating antibody, the patients lack lymphocytes corresponding to lepromin. Lepromatous patients also carry an enormous number of macrophages loaded with leprae bacilli. But for some unknown reason, the macrophages, that are supposed to engulf and destroy foreign organisms, are incapable of recognizing or destroying the leprae bacilli.

One approach to enhancing cell mediated immunity in lepromatous patients was undertaken by Ward E. Bullock, M.D., a NIAID grantee, James P. Fields, M.D., and Michael Brandriss, M.D., at the University of Rochester School of Medicine. The key to their study was a substance called transfer factor, which is a

(more)

product of sensitized lymphocytes of normal humans. In earlier studies, scientists found that transfer factor from an individual who was sensitive to a particular antigen could confer that sensitivity to the lymphocytes of a recipient who previously did not respond to the antigen. The investigators reasoned that transfer factor from normal individuals who had a high degree of delayed hypersensitivity to antigens of *M. leprae* might confer this sensitivity to lepromatous leprosy individuals.

In the study, which was reported in the November 23, 1972 issue of the *New England Journal of Medicine*, nine patients with lepromatous leprosy were given sensitized lymphocytes or transfer factor from persons with a high degree of delayed hypersensitivity to lepromin. The investigators induced weak systemic hypersensitivity in six of the nine patients--three who had received lymphocytes and three who had received transfer factor. They found that a single dose of transfer factor did not result in dramatic long-term clinical improvement in the patients. This was expected since these patients have such a depressed state of cellular immunity and so many bacilli.

This work was also supported by a General Clinical Research Center grant from the NIH Division of Research Resources.

A different and more successful approach was taken by Dr. Soo Duk Lim, an associate professor of dermatology at Seoul University, Korea, and visiting professor of pathology at the University of Minnesota in Minneapolis. Working closely with Robert A. Good, Ph.D., M.D., a NIAID grantee (and now president of Sloan-Kettering Cancer Institute in New York), Dr. Lim infused

(more)

14 lepromatous patients with massive doses of lymphocytes from unmatched donors weekly for periods of up to 16 weeks. By infusing mismatched lymphocytes, the scientists hoped to set up a limited graft vs. host reaction.

Theoretically, the immunocompetent but immunologically incompatible donor cells should recognize as foreign not only the recipient tissues but also the leprae bacilli. The result would be that the lymphocytes would spur the dormant macrophages to destroy their leprous invaders.

The treatment, used on patients who had failed to respond to other therapy, helped in all cases. The levels of bacilli in the tissues declined and the external lesions characteristic of the disease softened and decreased in size. After 16 weeks, Dr. Lim returned his subjects to conventional chemotherapy and all of the patients have been free of the disease to date. One person in the study has been followed for a year and a half with no sign of recurrence. Dr. Lim reported these findings at the Second International Workshop on the Primary Immunodeficiency Diseases in Man held in St. Petersburg, Florida in March.

Dr. Lim plans a controlled study to compare the effectiveness of this approach with chemotherapy and transfer factor. He cautions that physicians treating leprosy patients should not begin switching to this immunologic approach until it has been further tested. On the basis of preliminary evidence, however, it appears that this method will be of value in treating lepromatous leprosy and possibly other diseases where conventional chemotherapy has failed.

Photo Feature

Women in Research...

UNIVERSITY OF TEXAS INVESTIGATORS PROBE THE BIOMEDICAL SCIENCES

Edith D. Box, Sc.D., (above) an associate professor of microbiology at the University of Texas Medical Branch at Galveston (UTMB), is studying the life cycle of a coccidian parasite in birds, resembling the toxoplasmosis parasite in humans. Dr. Box, who has been at UTMB for 23 years, is supported by the National Institute of Allergy and Infectious Diseases. Betty Jean Williams, Ph.D., (right) monitors the polygraph recording of an isolated heart. She is supported by the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD). Rose G. Schneider, Ph.D., (below) has been a UTMB for 25 years. A resident professor of pediatrics, her studies of sickle cell disease and related conditions are funded by NIAMDD. (NIH Photos #1050, 1051, 1052)

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Medical News Tip

DIAGNOSIS VIA ULTRASOUND--Ultrasonography is a valuable technique for the diagnosis of eye diseases. This safe and rapid procedure yields unique information about the relationships between the structures of the eye and the surrounding orbit.

In ultrasonography, the patient's cornea is bathed in a saline solution and an ultrasound beam is directed into the eye. This beam scans the eye and is then reflected and sensed by a detector. The resultant signal is displayed on a television-type tube, thereby giving a "picture" of the reflected beam. The display on the tube is then photographed and interpreted.

D. Jackson Coleman, M.D., of Columbia University has published several reports based on three years experience with over 1,000 patients. He observed characteristic scan patterns for various eye diseases and formulated rules for diagnosing them. These were tested on 100 eye disease and 100 orbital disease patients and the diagnosis was verified by other tests or long-term follow-up.

For additional information contact:

National Eye Institute Information Office
Bldg. 31, Room 6A-27
Bethesda, MD 20014
Phone: (301) 496-5248

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New Publication:
Discovering Yourself in the Brain Age

A purpose of *Discovering Yourself in the Brain Age* is to encourage talented young people to consider the exciting and important field of brain research.

This publication contains a history of man's theories about the brain--including Aristotle's belief that the function of the brain was to cool the blood.

Also included is factual material from the National Institute of Neurological Diseases and Stroke about the anatomy and workings of the brain and nervous system.

Future brain scientists who are now in college are urged to study physics, biology, chemistry, psychology, and mathematics. The publication also lists 14 books which concentrate on the brain and brain research.

Science writers can obtain a free copy of this publication from:

NINDS Information Office
Bldg. 31, Room 8A-03
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Phone: (301) 496-5751

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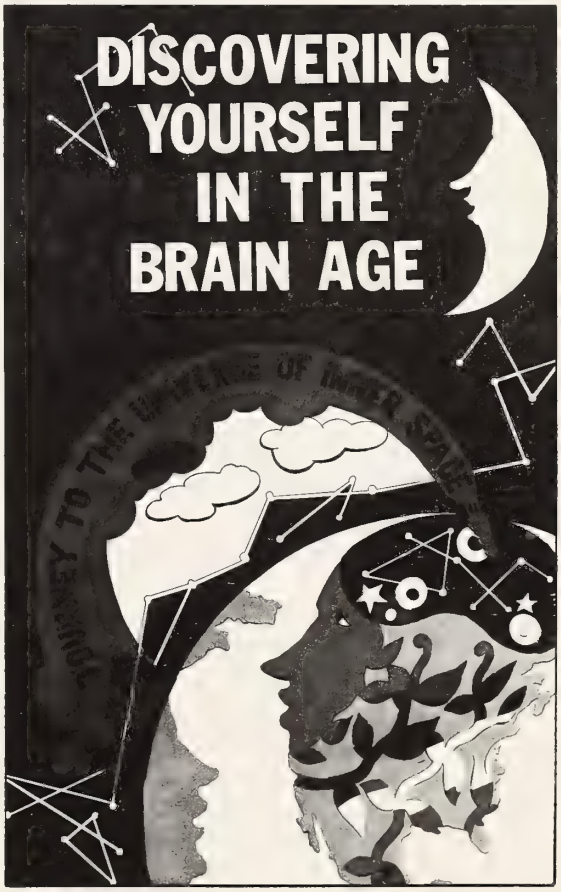

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NEWS&FEATURES FROM NIH

PORTFOLIO – PHARMACOLOGY & TOXICOLOGY

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE■Public Health Service■National Institutes of Health■Office of Information■Bethesda, Maryland 20014

(See Page Nine)

P/T

May 1973

NEWS&FEATURES FROM NIH

NIH PORTFOLIO ON THE PHARMACOLOGY-TOXICOLOGY PROGRAM....MAY 1973

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE■Public Health Service■National Institutes of Health■Office of Information■Bethesda, Maryland 20014

Marc Stern, Editor --- Carol M. Sussman, Associate Editor
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NIH News Branch, Building 31, Room 2B-10, Bethesda, MD 20014, [301] 496-1206

INTRODUCTION: NIH SUPPORTS RESEARCH IN PHARMACOLOGY AND TOXICOLOGY

The Pharmacology-Toxicology Program of NIH's National Institute of General Medical Sciences (NIGMS) is a unique, integrated national program. Its overall objective is to improve medical therapy through increased understanding of the principles and mechanisms of drug action and how this action is influenced by various factors. Research supported by this program is providing a rational basis for the safer and more effective use of presently available drugs and is contributing to the design of more effective therapeutic agents. Thus, this program, through its support of research, has significantly stimulated the field of pharmacology and toxicology and especially clinical pharmacology.

Pharmacology-toxicology studies have led to greatly expanded knowledge of the relationship between dosage, blood concentrations, and therapeutic or toxic effects; an understanding of factors determining the wide variability in response of different individuals to the same drug and dosage; as well as the interactions of drugs with other drugs, chemicals, diseases, and/or altered physiological states, such as pregnancy or malnutrition.

A new field which delineates the important influence of genetic factors on drug response is rapidly emerging. Also, it has become increasingly evident that the disease state itself may produce important changes in drug distribution, thus requiring another drug or a distinctly different dosage regimen in the proper treatment of the patient. In addition, important differences are appearing in the effects of drugs and how they are handled in the human fetus and neonate as compared with the adult and geriatric patient.

Furthermore, since the same principles and methodology are applicable to toxic agents, such as industrial poisons, pesticides, and environmental pollutants, there is a growing development of a far more sophisticated science of toxicology. Modern toxicology has the capability of predicting, attenuating, or even preventing disasters which result from the ubiquitous chemicals found in man's environment.

(more)

Information obtained in this program is of importance to the Food and Drug Administration and other groups, both public and private, in the study of the safety and efficacy of drugs in humans and animals.

The Pharmacology-Toxicology Program includes 11 centers, 10 program projects, 41 regular research projects, and four contracts.

The scope of this NIGMS research ranges from basic biological studies in molecular pharmacology through comparative studies in laboratory animals, to rigidly controlled clinical evaluation of drug efficacy in man. Long-range studies are also conducted on oral contraceptives, adverse drug reactions, drug-induced diseases, and factors influencing drug action.

One of the first-line approaches to accomplishing the objectives of the program has been to encourage quantitative pharmacology in terms of precise measurements of drugs and their metabolites and to develop highly sensitive and specific quantitative methods to determine the levels of these chemicals in such biological specimens as blood, urine, cerebrospinal fluid, and tissues.

The strategy has been to concentrate on (1) drug metabolism, that is, what happens to a drug or chemical once it enters the blood stream; (2) the development of necessary instrumentation and methodology; (3) the establishment of cohesive and collaborative working units (centers and program projects); (4) a more thorough understanding of the biochemical mechanisms of drug action; (5) the interaction of drugs with chemicals, other drugs, and diseases; (6) the understanding of human variability in the response to drugs; and (7) the application of such knowledge to therapeutic problems in man.

[See *New Areas of Research* on page 20 of this Portfolio.]

This Introduction was prepared by Byron B. Clark, Ph.D., Program Director of the Pharmacology-Toxicology Program of the National Institute of General Medical Sciences (NIGMS). NIGMS is a component of the National Institutes of Health, an agency of the U. S. Department of Health, Education, and Welfare.

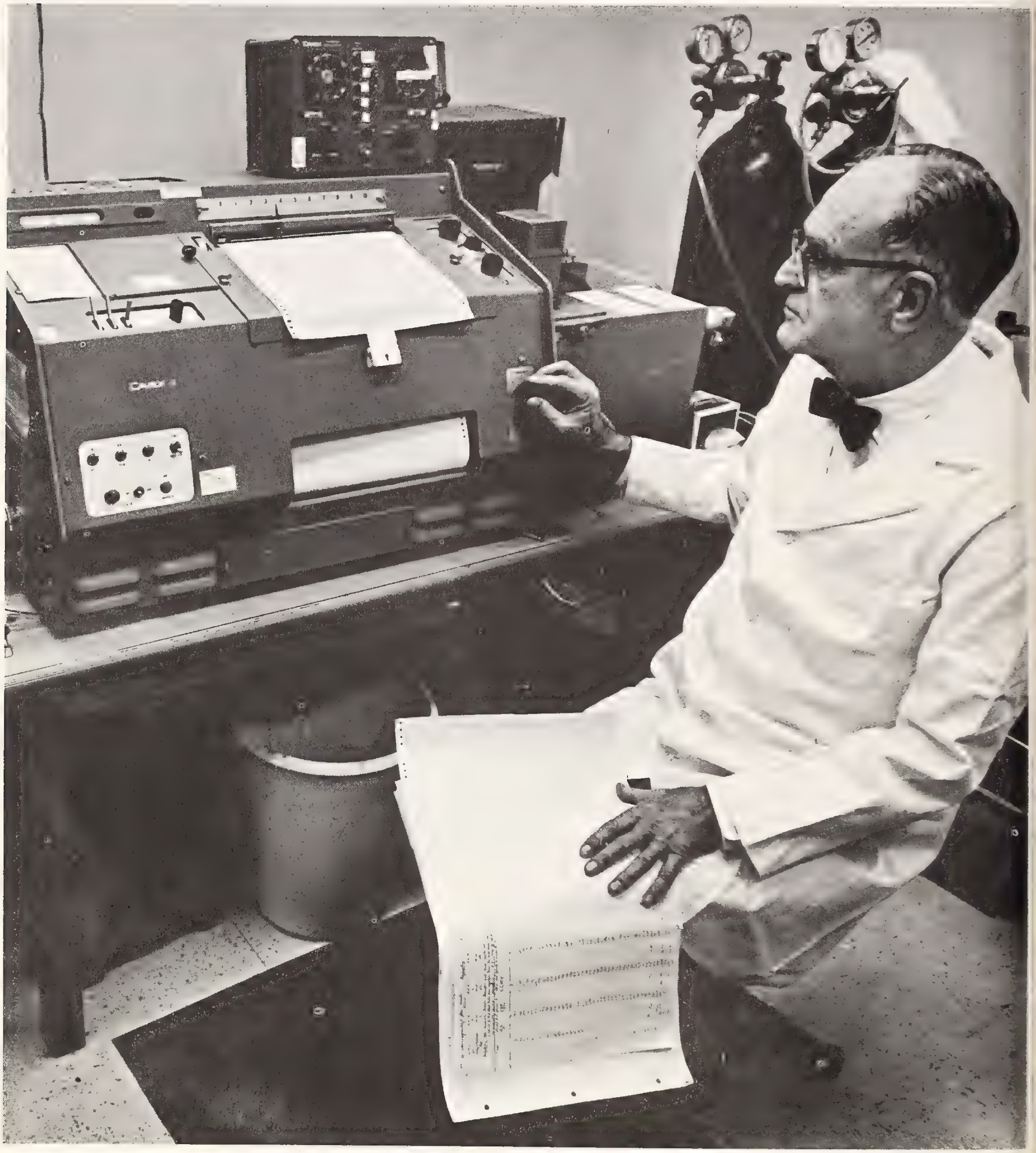
ANN ARBOR, MI--Edward A. Carr, Jr., M.D., and research associate Mary Carroll, examine radioisotope cardiac scans of a heart transplant patient who has been monitored for more than four years at the University of Michigan Medical Center. According to Dr. Carr, director of the Upjohn Center for Clinical Pharmacology at the University, the scans, which measure myocardial uptake of radioactive cesium, have accurately indicated several episodes of rejection confirmed by other physiological indications. The NIH Pharmacology-Toxicology Program is supported by the National Institute of General Medical Sciences. (NIH Photo #T-1)

ATLANTA, GA--John L. McNay, M.D. (left), and Leon I. Goldberg, M.D., Ph.D., Director, Emory University Clinical Pharmacology Program, examine a patient. Dr. Goldberg's research on drug metabolism in man, hypertensive drugs, and pediatric pharmacology is supported by the National Institute of General Medical Sciences through the Pharmacology-Toxicology Program. (NIH Photo #T-2)

BALTIMORE, MD--Paul Talalay, M.D., examines a mass spectrometer printout with Catherine Fenselau, Ph.D., as part of his research on schistosomiasis at the Johns Hopkins University School of Medicine. Dr. Talalay's project, "Design of Chemotherapeutic Agents," is part of the NIH Pharmacology-Toxicology Program, supported by the National Institute of General Medical Sciences. (NIH Photo #T-3)

BOSTON, MA--Hershel Jick, M.D. (left) and Dennis Slone, M.D., co-directors of the Boston Collaborative Drug Surveillance Program of Boston University Medical Center, analyze information on the therapeutic and adverse effects of commonly used medications. Researchers at hospitals in the United States, Canada, England, Israel, and New Zealand have contributed data on about 15,000 of their patients. The NIH Pharmacology-Toxicology Program supports this research through the National Institute of General Medical Sciences. (NIH Photo #T-4)

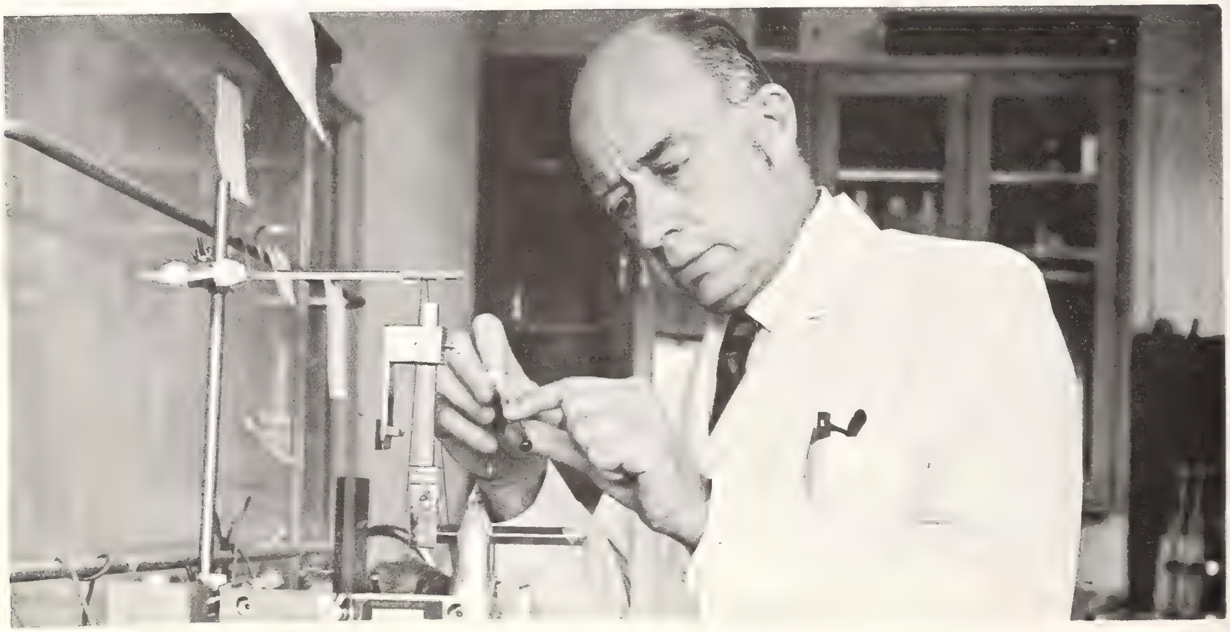
CHAPEL HILL



CHAPEL HILL, NC--Thomas Butler, M.D., of the University of North Carolina studies results of an experiment in his research on penicillin sensitivity. The National Institutes of Health supports the Pharmacology-Toxicology Program through the National Institute of General Medical Sciences. (NIH Photo #T-5)

CHARLESTON, SC--Thomas E. Gaffney, M.D., professor and chairman of the Department of Pharmacology at the Medical University of South Carolina, evaluates a chemical sample as part of his research into the clinical pharmacology of antiarrhythmic drugs. The Pharmacology-Toxicology Program is supported by the National Institutes of Health through the National Institute of General Medical Sciences. (NIH Photo #T-6)

DALLAS, TX--Ronald W. Estabrook, Ph.D., chairman of biochemistry at the University of Texas Southwestern Medical School and Brenda W. Griffin, Ph.D., investigate hepatic microsomal drug oxidation. The NIH Pharmacology-Toxicology Program is supported by the National Institute of General Medical Sciences. (NIH Photo #T-7)



GAINESVILLE, FL--Thomas H. Maren, M.D., professor and chairman of the Department of Pharmacology at the University of Florida J. Hillis Miller Health Center, evaluates an antimalarial drug. Dr. Maren's research is supported by the National Institutes of Health through the Pharmacology-Toxicology Program of the National Institute of General Medical Sciences. (NIH Photo #T-8)

HOUSTON, TX--Marjorie G. Horning, Ph.D., professor of biochemistry, monitors computer data tabulation in her research at Baylor College of Medicine on perinatal pharmacology. Some of the other scientific equipment that she uses in this research was developed by her husband, Evan C. Horning, Ph.D., who is studying human biochemistry under an NIH research grant. The NIH Pharmacology-Toxicology Program is supported by the National Institute of General Medical Sciences. (NIH Photo #T-9)

IOWA CITY, IA--Thomas R. Tephly, M.D., Ph.D., professor and director of The Toxicology Center, The University of Iowa, studies the structure and function of the enzyme P-450 in rats. The enzyme is important in the metabolism of a wide variety of drugs and toxicants. Dr. Tephly has been studying the enzyme for about seven years, demonstrating the role of the heme part of the molecul in the regulation of its action. He also is working on ways to reverse processes and symptoms which accompany certain diseases of heme metabolism. The NIH Pharmacology-Toxicology Program is supported by the National Institut of General Medical Sciences. (NIH Photo #T-10)

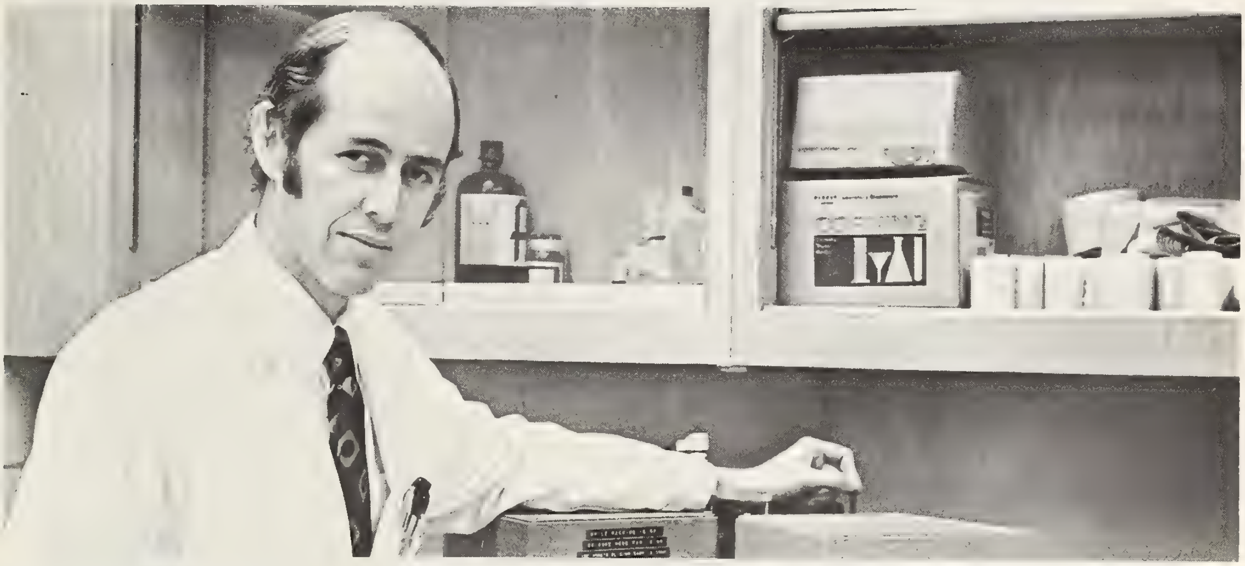
KANSAS CITY

KANSAS CITY, KS--Daniel L. Azarnoff, M.D., professor of medicine and pharmacology and chief of the section of clinical pharmacology at the University of Kansas Medical Center, uses a high pressure liquid chromatograph to assay drugs as part of his research on clinical pharmacology, drug metabolism, absorption, and cancer detection. The NIH Pharmacology-Toxicology Program is supported by the National Institute of General Medical Sciences. (NIH Photo #T-11)

LOS ANGELES, CA--Carl M. Pearson, M.D., researches clinical pharmacology in rheumatic and muscular diseases in his laboratory at the University of California, Los Angeles, School of Medicine. The NIH Pharmacology-Toxicology Program is funded by the National Institute of General Medical Sciences. (NIH Photo #T-12)

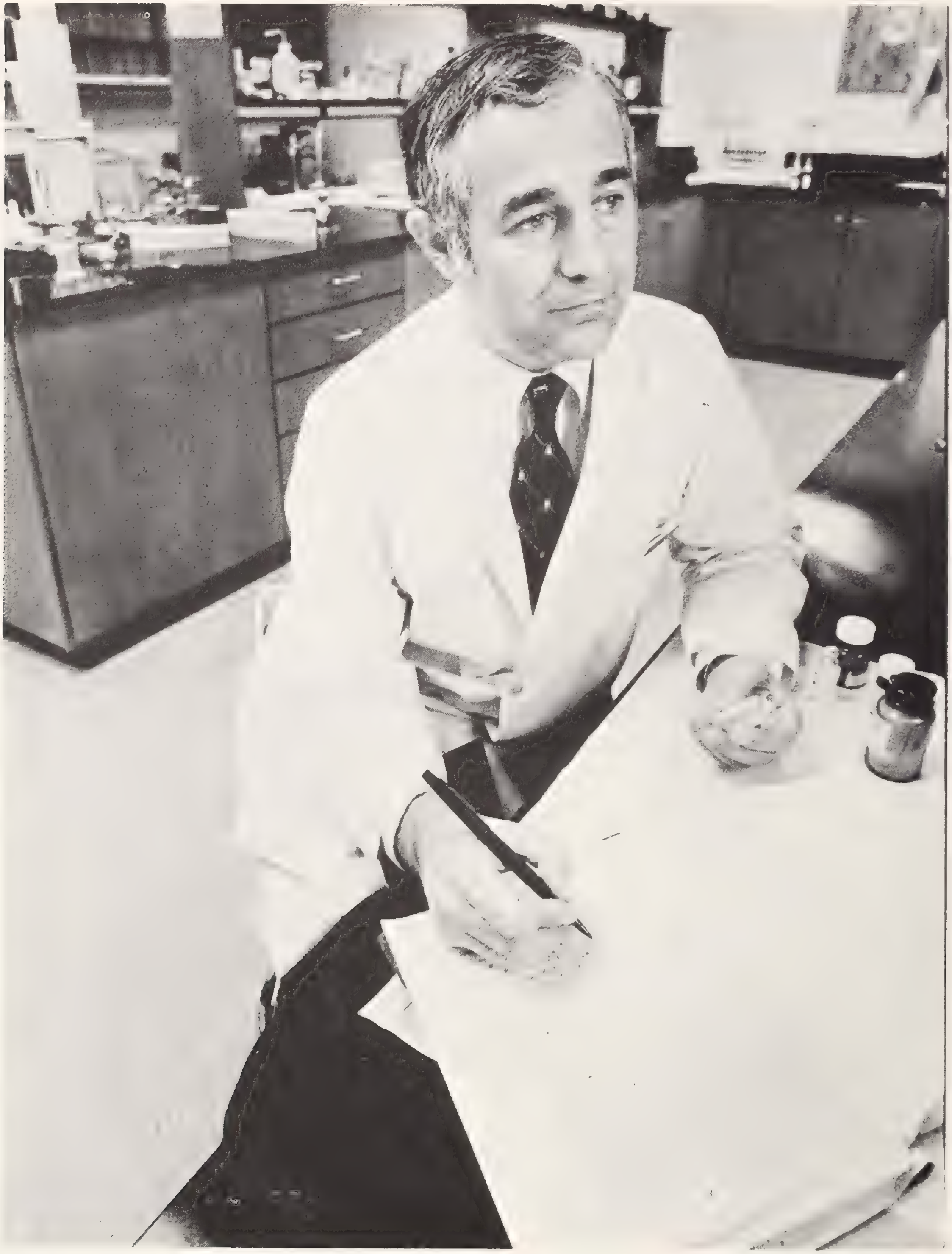
MINNEAPOLIS, MN--Gilbert J. Mannering, Ph.D., of the University of Minnesota studies graphic printout in his research on biochemical pharmacology and pediatric pharmacology. The NIH Pharmacology-Toxicology Program is supported by the National Institute of General Medical Sciences. (NIH Photo #T-13)

NASHVILLE, TN--Charles D. Proctor, Ph.D., professor and chairman of the department of pharmacology of Meharry Medical College investigates nutritional factor effects on drug action. Dr. Proctor's research on the effect of nutrition on amphetamine metabolism is supported by the National Institutes of Health through the Pharmacology-Toxicology Program of the National Institute of General Medical Sciences. (NIH Photo #T-14)



NASHVILLE, TN--John A. Oates, M.D., of Vanderbilt University uses a spectrophotofluorometer in his research on drug metabolism, hypertension, and prostaglandins in man. The NIH Pharmacology-Toxicology Program is funded by the National Institute of General Medical Sciences. (NIH Photo #T-15)

NEW YORK, NY--Bert N. La Du, Jr., M.D., Ph.D., of the New York University, is investigating hereditary variations in man which modify drug toxicity. His work on genetics and drug metabolism is supported by the National Institute of General Medical Sciences through the NIH Pharmacology-Toxicology Program. (NIH Photo #T-16)



PROVIDENCE, RI--Paul Calabresi, M.D., principal investigator of the clinical and biochemical pharmacology program at Brown University, evaluates an anticancer drug. The NIH Pharmacology-Toxicology Program is supported by the National Institute of General Medical Sciences. (NIH Photo #T-17)

RESEARCH TRIANGLE PARK, NC--David Rosenthal, Ph.D. (left) and Monroe E. Wall, Ph.D., director, chemistry and life sciences division, Research Triangle Institute, calibrate an LKB mass spectrometer connected with an alternating voltage accelerator device for use in the estimation by mass spectrometry of carbon-13 labeled drugs and their metabolites. This drug research at the Institute is part of the NIH Pharmacology-Toxicology Program, which is supported by the National Institute of General Medical Sciences. (NIH Photo #T-18)

ROCHESTER, NY--Thomas W. Clarkson, Ph.D., professor at the University of Rochester School of Medicine and Dentistry, checks the levels of total organic and inorganic mercury in samples of hair taken from an individual who may have been exposed to the metal. Dr. Clarkson is principal investigator in the Center for Toxicological Research of the University. The NIH Pharmacology-Toxicology Program is supported by the National Institute of General Medical Sciences. (NIH Photo #T-19)

SAN FRANCISCO, CA--Kenneth L. Melmon, M.D., project director for the Pharmacology-Toxicology Program at the University of California, San Francisco, checks results of his staff's research on pharmacokinetics. NIH's Pharmacology-Toxicology Program is funded by the National Institute of General Medical Sciences. (NIH Photo #T-20)

◀ *MILAN, ITALY--Dr. Silvio Garattini, M.D., Director, Istituto di Ricerche Farmacologiche, "Mario Negri," examines results of an experiment in his study of effects of drugs on aging and behavior. Dr. Garattini's* research is supported *by the NIH Pharmacology-Toxicology Program through the National Institute of General Medical Sciences.*

NEW AREAS OF RESEARCH

[See *Introduction* on pages two and three of this Portfolio.]

Pharmacogenetics--Inherited variations in an individual's response to drugs result in a demand for different dosage regimens in individuals with impaired drug deactivation (termination) ability. For example, the antitubercular drug isoniazid is deactivated by acetylation. There are genetically two populations --one rapid acetylators and the other slow acetylators. Thus different dosage regimens are required to achieve effectiveness and avoid toxicity.

Perinatal Pharmacology--Basic differences between infant and adult responses to drugs, such as those related to drug-metabolizing enzyme systems, are being elucidated. Most drugs pass the placenta and may be found in the plasma and urine of the newborn. Using gas-liquid chromatograph-mass spectrometer computer techniques, the drugs can be specifically identified in plasma or urine of the infant regardless of the patient history. Without physician approval, some pregnant women take aspirin, sedatives, caffeine, or even narcotics prior to delivery. These studies will lead to a better understanding of drug action in infants and the prevention of birth defects and postnatal sequellae.

Immunopharmacology--The emerging area of research on immunosuppressive drugs will be of importance in organ transplantation and control of allergic reactions and may contribute to the alleviation of arthritis, systemic lupus, and other collagen and autoimmune diseases. Further information is needed on the role of drugs in various allergic processes, such as phototoxicity.

Program in Stable Isotopes--A cooperative effort with the Atomic Energy Commission has permitted the increased production of drugs labeled with stable isotopes of carbon, oxygen, nitrogen, and sulfur. Such drugs as dilantin, phenobarbital, and progestational steroids are being synthesized and labeled with carbon 13 for pediatric and perinatal pharmacology research. Stable isotopes are also useful as internal markers for mass spectrometry.

Analytical Aspects--New instrumentation is being developed to permit selective analysis of minute quantities of drugs and their metabolites in blood and tissue with the objective of developing improved simplicity, sensitivity, and specificity. These studies should lead to automated procedures adapted to the clinical laboratory suitable for monitoring therapeutic plasma levels of drugs and the detection of inadvertent drug ingestion and narcotics in patients. This applies also to radio-immunoassay procedures with potential for great sensitivity and specificity.

Drug Surveillance--A major effort is the Boston Collaborative Drug Surveillance Program, a specialized multidisciplinary epidemiological study to detect the incidence of adverse reactions, as well as drug efficacy, for purposes of assessing the risks in drug therapy.

Pharmacotherapeutics--New therapeutic approaches will lead ultimately to clinical trials in conjunction with the basic research programs.

NEWS&FEATURES FROM NIH

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE ■ Public Health Service ■ National Institutes of Health ■ Office of Information ■ Bethesda, Maryland 20014

May 25, 1973

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NOTE TO SUBSCRIBERS:

In June, the National Institute of Dental Research (NIDR) will celebrate its 25th Anniversary. Planned events include a scientific conference on dental research at the Washington Hilton, June 28 and 29. A press kit for science writers will be available.

NEWS & FEATURES From NIH *is devoting the Research Advances section in this issue exclusively to articles about NIDR-supported research. Science writers can obtain additional information about the Institute by contacting:*

NIDR Information Office
Bldg. 31, Room 2C-33
NIH, Bethesda, MD 20014
Phone (301) 496-4261

#

Research Advances

Studies in Rats...

VACCINATION AGAINST TOOTH DECAY SUCCEEDS IN SOME EXPERIMENTS

Experimental vaccination against tooth decay has generally produced disappointing results. Now, a team of dental scientists from the NIH National Institute of Dental Research (NIDR) and the University of Connecticut Health Center report encouraging--although variable results--in a new study.

Jason M. Tanzer, D.M.D., George J. Hageage, Jr., Ph.D., and Rachel H. Larson, Ph.D., report that they attempted to immunize rats against Streptococcus mutans, a bacterium which has been strongly implicated as a prime decay-causing microorganism in human mouths. In three separate experiments, the immunization apparently protected the rats at least partly against tooth decay caused by Streptococcus mutans.

While the investigators viewed the apparent immunization as exciting and hopeful, they cautioned that they failed to immunize the rats in some of the experiments.

Additionally, other aspects of the experimental results troubled the scientists and indicated that immunization against tooth decay is a complicated and difficult problem.

For example, although the salivary antibody apparently could inhibit the decay caused by Streptococcus mutans, it did not destroy these bacteria nor did it make the plaque disappear from the teeth.

Furthermore, small sores developed in the skin at the point of the immunizing injections. However, these sores did not seem to trouble the

(more)

rats since the immunized animals ate and grew apparently as well as the non-immunized rats.

The variability between experiments is puzzling, according to the investigators. They chose rats as the model for the immunization attempts because these animals, like humans, develop severe tooth decay when infected by Streptococcus mutans. Usually when kept on high-sugar diets, the animals develop decay only on the chewing or grinding surfaces of the teeth. However, when rats are infected by Streptococcus mutans, they not only get severe decay of the chewing surfaces, but also develop severe decay on the smooth surfaces of the teeth.

The aim of the study was to make the rats resistant to decay by producing antibodies to Streptococcus mutans. Consequently, injections of killed Streptococcus mutans were given under the skin of test animals prior to their infection by bacteria. Other rats were infected but not given the immunizing injections. Other control rats were neither infected nor injected.

Tests showed that the immunized rats developed high levels of antibody in the blood as expected and also developed antibody in the saliva. According to the investigators, this is important because salivary antibody is probably the only antibody that can reach the decay-producing bacteria which live on the tooth surfaces in an adhesive coating called plaque.

The researchers, while expressing guarded optimism about immunizing against decay, indicated that much more must be learned before this goal can be considered practical for humans.

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Dr. Tanzer, of the University of Connecticut, and Drs. Hageage and Larson, of NIDR, presented their findings at the International Association for Dental Research meeting held April 14, 1973 in Washington, D.C.

#

Research Advances

In Periodontal Disease...

MAST CELLS PLAY KEY ROLE IN DESTRUCTION OF TISSUE

A process in which collagen is destroyed through actions of the mast cells may account for some of the tissue destruction characteristic of periodontal disease.

According to National Institute of Dental Research grantee A. Cecil Taylor, Ph.D., the mast cell appears to hold a key to the breakdown of collagen in the presence of serum. Mast cells are granular cells present in connective tissue.

Dr. Taylor, of the Texas Medical Center at Houston, notes that large amounts of collagen, the chief protein in connective tissue, are lost in periodontal disease. There is a certain amount of collagen turnover in the normal course of wear and repair, but only in certain specific diseases of bone, joint, and some other tissues does rapid destruction of large amounts of collagen occur.

Speaking at the International Association for Dental Research meeting on April 14, 1973, in Washington, D. C., Dr. Taylor discussed his study of the destruction of the long protein molecule by an enzyme called collagenase.

The investigator found that he could harvest collagenase from cultures of gingival cells for about a week after the tissues have been removed from the mouth. In the laboratory, this enzyme will readily digest collagen fibers from a variety of sources provided no serum is present.

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In life, however, serum is present throughout most of the body. Consequently, Dr. Taylor directed his attention to identifying what mechanism could either turn on the enzyme when it is needed, turn off an enzyme inhibitor in serum, or perhaps serve as a trigger or co-factor to start digestion of collagen.

Dr. Taylor noted that collagenase from rat gingival cells always digested mesenteric collagen (the thin layer of tissue that supports the intestines) when serum was absent. However, when two to 50 percent of serum was added to the medium, the only areas of digested collagen appeared as clear rings around mast cells.

When the same treatment was given to rat tendon which lacked mast cells, no collagen was destroyed until mast cells were added to the preparation.

Extracts of other cells (white blood cells, muscle, kidney, and liver) did not trigger collagen digestion. Similarly, some of the special substances produced by mast cells (heparin, histamine, and serotonin) failed to trigger collagen digestion.

Dr. Taylor believes that the trigger substance, which is not yet identified, is released only when the granules in mast cells are broken up.

Because its activity is not destroyed by heat, it is probably not an enzyme. And because it is packaged in granules within a relatively rare type of cell, it is obviously under close control most of the time, he adds.

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However, the fact that granules are released from mast cells by allergic reactions suggests that allergic reactions in the mouth might also release the substance that allows collagenase to destroy collagen in the presence of serum. And, Dr. Taylor concludes, this process could account for some of the tissue destruction occurring in gum disease.

#

Research Advances

SPECIAL IODINE SOLUTION REMOVES DENTAL BACTERIA

Selective chemical control may help eliminate a prime bacterial suspect in the tooth decay process.

According to Ronald J. Gibbons, Ph.D., of the Forsyth Dental Center, Boston, the bacterium known as Streptococcus mutans lives only in a few specific locations, preferably where teeth adjoin or in crevices in chewing surfaces. Additionally, the bacteria is very slow to spread from tooth to tooth. Dr. Gibbons reports that the use of a special iodine solution (Lugol's) led to the elimination of the bacteria in some test subjects. His research is supported by the National Institute of Dental Research.

Dr. Gibbons reasoned that if Streptococcus mutans could be totally removed from its preferred ecological niches, the children who harbor this infection should remain free of danger from tooth decay for a long period of time.

In his study, he monitored four interproximal areas (between teeth) for occurrence of the bacterium during five consecutive weeks in 20 children. The investigator found that some subjects consistently harbored the organism in all four places while others harbored it in fewer or even just one spot with an equal consistency.

In the study, Dr. Gibbons cleaned all the children's teeth and painted a special iodine solution on the four selected areas in 10 children. In the control group, he used a salt solution.

The investigator took bacterial samples after 30 minutes and then at intervals up to 13 weeks. According to Dr. Gibbons, Streptococcus mutans

(more)

continued to grow in the control children. In four subjects of the iodine treated group, the organism was also found alive 30 minutes after the iodine application and then continued as usual. However, the iodine wiped out the bacteria in six of the youngsters. These children remained free of the infections in those areas for at least 13 weeks.

Dr. Gibbons was assisted in the study by Paul F. DePaola, D.D.S. and Diane M. Spinell. He reported the findings of this study at the International Association for Dental Research meeting in Washington, D.C., April 14, 1973.

#

Photo Feature

NEW ULTRASONIC CAMERA OBSERVES SOFT TISSUES

An ultrasonic camera now being developed can display live television images of internal organs and other soft tissues that are invisible to X-rays. Scientists anticipate that the camera will prove effective for detecting heart disease, cancer, and other diseases, as well as for observing the movement of the human fetus without the danger that accompanies X-rays.

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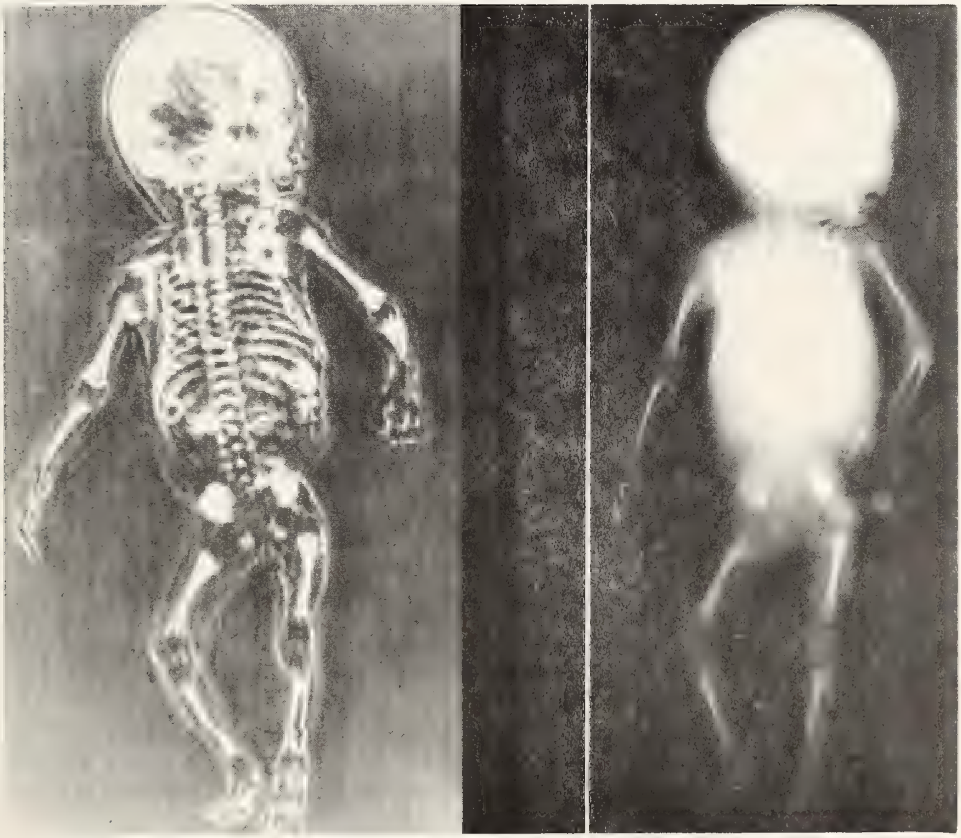

The picture of a 17-week-old human fetus on the right was obtained by conventional X-ray method. The picture of the same fetus on the left was taken with ultrasonic rays. An ultrasonic camera, developed under a National Institute of General Medical Sciences grant, will produce ultrasonic images like this of internal organs without the danger that accompanies X-rays. (NIH Photo #1053)

Ultrasonic Camera (Cont'd)

The ultrasonic system, developed at the Stanford Research Institute (SRI) under a grant from the National Institute of General Medical Sciences, has a number of important advantages over its X-ray counterparts, particularly for viewing soft internal organs.

Unlike the X-ray, the ultrasonic system produces no ionizing radiation. As a result, it is expected that the system can be used safely for continuous and repeated periods of observation, making it possible to follow the course of a disease without danger to the patient.

Also, the ultrasonic camera can view internal organs without the injection into the bloodstream of the special contrast material necessary for an X-ray system. The inherent risk involved in such injections limits the usefulness of the X-ray as a tool for mass screening.

Although ultrasonic waves at very high intensities can cause tissue damage, tests indicate that the relatively low energy levels required for diagnostic purposes are completely safe.

The ultrasonic camera works in a manner similar to a television camera, imaging the object with sound waves instead of light. The sound waves scattered in the body are collected with a special lens and brought to focus. Instead of putting film in the focal plane, ultrasonic sensors are used to convert the sound to electrical signals for a television display. The camera uses ultrasonic frequencies that are about 200 times higher than the highest sounds the human ear can hear.

(more)

While the ultrasonic camera has a number of important advantages over X-rays, it is being designed to supplement rather than replace X-ray systems. Using a prototype of the camera system, SRI scientists have observed muscle fibers, tendons, and blood vessels in the arms and legs and excised organs such as the kidney and brain. However, X-rays are preferable for viewing dense material such as bone.

Similar to a fluoroscope, the system reveals the motion of internal organs. The physician brings the ultrasonic camera into contact with the patient's body and examines the resulting pictures on a TV monitor. The sound energy is coupled to the patient's skin through a flexible water-filled chamber.

One type of ultrasonic system now in use in medical clinics produces a flat, cross-sectional image like a radar display. By contrast, images produced by the new system are similar to X-rays.

The SRI camera system is now being packaged for clinical trials and should be available in about six months.

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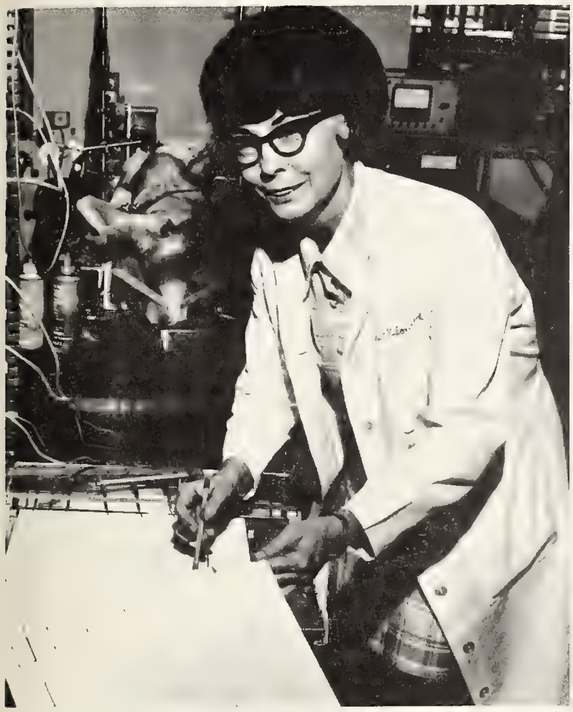
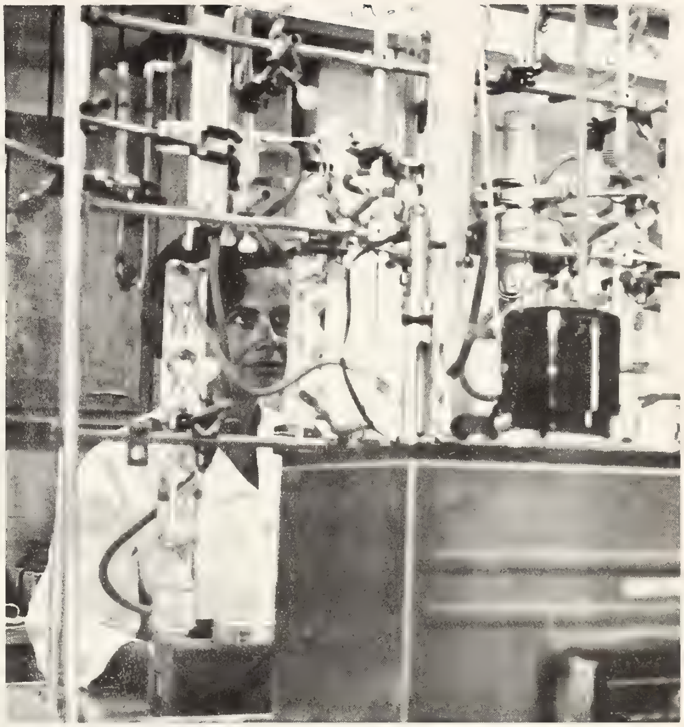
Research Advances

Women in Research...

SOUTH CAROLINA SCIENTISTS STUDY DIABETES, HEART DISEASE





At the Medical University of South Carolina, Maria G. Buse, M.D. (above) studies the factors that modify the action of insulin. A professor of medicine, Dr. Buse has been supported by the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) for 15 years. She is primarily interested in the effect of diabetes on the metabolism of muscles, nerves, and the heart. Margaret Clapp Conrad, Ph.D. (top, right) is a professor of physiology at the University. Here she is shown recording circulatory and respiratory effects of fluid aspiration in the anesthetized dog. Dr. Conrad is supported by the National Heart and Lung Institute. Hulda J. Wohltmann, M.D., a professor of pediatrics, has been at the University for over six years. At right she is shown transferring frog muscle. Dr. Wohltmann is also a grantee of NIAMDD. (NIH Photos #1054, 1055, 1056) #

Photo Feature

CYCLIC AMP INITIATES GROWTH OF SLIME MOLD ORGANISM

University of Chicago scientists have confirmed a new, extra-cellular role for cyclic AMP (adenosine monophosphate). They have shown that it will initiate the aggregation of slime mold amoebae which become the multi-cellular slime mold organism.

Slime molds are relatively primitive, barely visible forms of life usually found in damp places. In their multi-cellular form, they start as small lumps and grow into cylindrical organisms. Their tip, or growing end, exudes a slime that hardens and forms an outer cover.

The behavior of slime mold cells when cyclic AMP is electrically pulsed from a microelectrode near them resembles the aggregating behavior of cells forming blood vessels in chick embryo cells, according to Anthony D.J. Robertson of the University of Chicago.

Mr. Robertson, Morrel H. Cohen, Ph.D., and other University of Chicago scientists believe that slime molds are a model for the aggregation of the cells in the embryos of higher organisms. They suggest that aggregation in embryos may be initiated by chemical signals consisting of pulsed cyclic AMP or other "chemical transmitters." Their research is supported by NIH's National Institute of Child Health and Human Development.

Robertson sees a parallel between the manner in which the slime mold cells react to diffusible transmitters and the way in which the nervous system could have developed from developmental control systems in the embryo. He believes it has potential application to adult brain physiology and cybernetics.

(more)

Slime molds (Cont'd)

In observing the reaction of slime mold amoebae to cyclic AMP through the use of time lapse photomicrographs and videotaped sequences, Robertson and his associates found that the slime molds react to periodically pulsed cyclic AMP in a wave-like, aggregating motion. Each pulse of the cyclic AMP sets up a relay reaction in the cells by which they in turn apparently emit cyclic AMP, after a slight time lag.

The effect of this chemical messenger is to attract neighboring cells to each other. This process of mutual self-attraction occurs in waves that are clearly visible in speeded-up time lapse films.

The relayed chemical signals cause the aggregation of some slime molds into spirals or branches, each receiving its basic signal from a single, dominant area in the growing multi-cellular organism. The dominant amoebae in the slime mold join together in the tip or "nipple" of the microscopic (1 mm.) slime mold. According to Robertson, the nipple appears to correspond to the "organizer" cells that dominate the formation of embryonic tissues in higher forms of life.

Robertson's research involves studies of *Dicytostelium discoideum*, one of many species of slime molds. Because the amoebae were deprived of their normal diet of bacteria, they entered into an intermediate phase before aggregating under influence of cyclic AMP.

The Chicago scientists hypothesize that slime molds aggregate in response to cyclic AMP signals originally emitted at about five-minute intervals from single cells and then continuously from the organism's dominant "tip" or "organizer" cells.

(more)

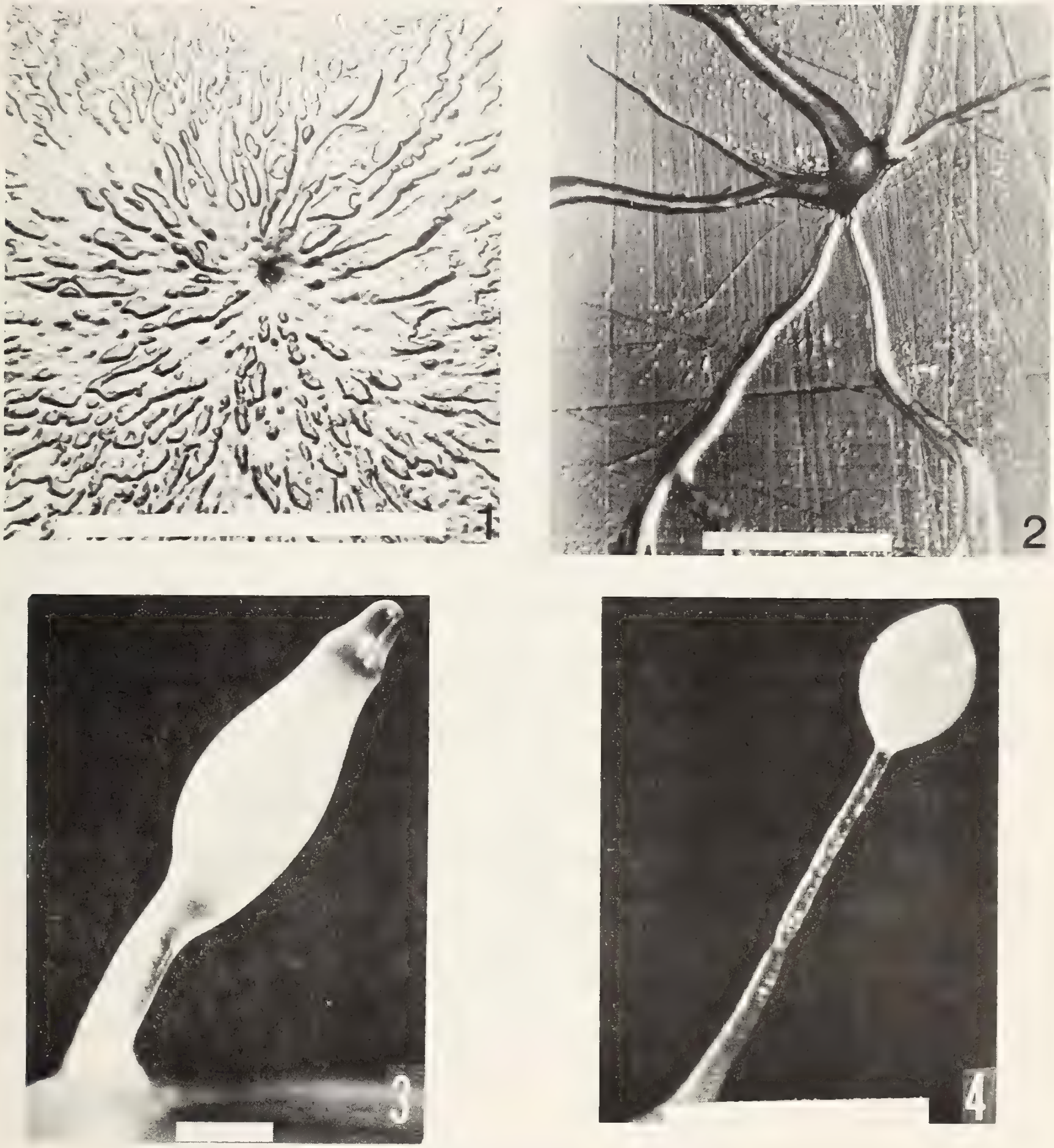
Slime molds (Cont'd)

Robertson presented a report of his findings at the American Chemical Society meeting in Dallas, April 11, 1973 and at a meeting of the American Physical Society in Cortland, New York, April 13, 1973.

(more)

Anthony D.J. Robertson, a University of Chicago biologist, stands in front of a composite of a number of electron micrographs of the slug, a multi-cellular form of a slime mold. Robertson hypothesizes that a transmitter such as that of cyclic AMP, which causes the aggregation of individual slime mold cells into a multi-cellular organism, is found in many higher forms of life, including humans. This research is supported by the National Institute of Child Health and Human Development. (NIH Photo #1057)

Slime Molds (Cont'd)



Slime molds, single-cell amoebae **that** *aggregate and form multi-cellular organisms, offer parallels to the manner in which cells come together in embryos to form tissue in higher life forms.* Photo (1): *Amoebae begin aggregating in response to a chemical "signal" from the "tip", shown at center of photo. (The length mark indicates 1 mm.)* Photo (2): *Six hours later, the migrating slime mold slug results from the aggregation process and emits a slimy material which hardens. (Length mark indicates 1/2 mm.)* Photo (3): *The slime mold enters its fruiting phase about three hours later. (Length mark indicates 1/10 mm.)* Photo (4): *Eight hours later, the fruiting body is seen with its stalk and spherical spore mass. (NIH Photos #1058, 1059, 1060, 1061).*

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NEWS & FEATURES From NIH May 25, 1973

Medical News Tip

NON-SURGICAL TECHNIQUE REMOVES MASSIVE EMBOLISM--In pulmonary embolism, a fairly common complication of inflammatory disease of the veins, bloodflow to the lungs is reduced by migrating blood clots that lodge in the pulmonary blood vessels.

In many cases, pulmonary embolism is effectively treated with supportive care and anticoagulant therapy. However, if the embolus is massive, it may cause the lungs to collapse and result in death from respiratory failure. In such instances, measures such as surgery to remove the clot may be applied, but overall mortality has remained high.

National Heart and Lung Institute (NHLI) grantees report successful use of a non-surgical technique for removal of massive pulmonary embolisms. The grantees used a stainless steel vacuum cup attached to a balloon-tipped catheter. This technique requires only local anesthesia and spares the critically-ill patient the stresses and hazards of major chest surgery.

In five of the six study patients, the clots were successfully removed with the catheter technique. After removal by suction, the patients' elevated pulmonary artery pressure fell to normal and their heart functions improved.

For information about NHLI research in this area, contact:

NHLI Information Office
Landow Building, Room C-918
Bethesda, MD 20014
Phone (301) 496-4236

#

New Publications

Seven fact sheets, each describing a common visual condition or cause of blindness, are now available from NIH's National Eye Institute.

Each fact sheet is written for the general public and describes the condition, its cause (if known), treatment (if available), and current research. The fact sheets are listed below:

Glaucoma--a disease characterized by loss of visual function associated with increased pressure within the eye and subsequent damage to the optic nerve.

Diabetic Retinopathy--a disturbance in the blood vessels of the retina, the light-sensitive tissue at the back of the eye, stemming from diabetes which can cause blindness.

Corneal Disease--often very painful disorders which affect the transparent membrane at the front of the eye.

Macular Degeneration--a common cause of visual disability among the elderly that affects a small part of the retina called the macula which is responsible for fine or reading vision.

Refractive Errors--nearsightedness, farsightedness, and other conditions that can usually be corrected with glasses or contact lenses.

Retinal Detachment--a separation of the layers of the retina that can cause permanent impairment of vision.

Retinitis Pigmentosa--an inherited disease involving progressive loss of peripheral vision beginning in childhood or adolescence.

Science writers can obtain a free copy of any or all of the seven fact sheets from the Office of Information, National Eye Institute, National Institutes of Health, Bethesda, MD 20014.

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NEWS & FEATURES From NIH June 10, 1973

Research Advances

AMNIOTIC FLUID TRANSFERS NUTRIENTS TO THE FETUS

The amniotic fluid which surrounds the fetus may serve as a vehicle for the administration of nutrients, drugs, or other compounds of potential benefit to the growing fetus.

Donald Orlic, Ph.D., and Robert Lev, M.D., of the New York Medical College recently reported this finding from their studies of fetal absorption of iron from swallowed amniotic fluid in the rat.

Dr. Orlic is associate professor of anatomy and Dr. Lev is associate professor of pathology at the Medical College. Their work is supported by the National Institute of Child Health and Human Development and by the National Institute of Arthritis, Metabolism, and Digestive Diseases.

In their studies, Drs. Orlic and Lev injected radioactive iron into the amniotic sacs of near-term rat fetuses. The investigators found that the iron in the amniotic fluid was swallowed by the fetuses. Within one to six hours following injection, the iron was detected in the intestine, liver, and spleen. Additionally, radioautographic studies showed that the iron had been incorporated into the epithelium of the intestine and liver of the fetus. The investigators also found that the developing red blood cells in the liver and spleen were heavily labelled with iron, as were some immature circulating red cells.

Previous studies by these investigators indicated that macromolecular protein is also absorbed by the fetal intestine following its injection into the amniotic sac. Their recent findings indicate that substances added

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to the amniotic fluid may be readily transported from the intestines to the circulation for use in developing organs.

The investigators also report that the membranes surrounding the developing rat fetus were also labelled with the injected radioisotope. They concluded that these yolk sac membranes, which are not found in human fetuses, were probably a second route by which the rat fetuses received radioiron.

Drs. Orlic and Lev plan to extend their investigations of fetal intestinal absorption of injected compounds to higher species such as the monkey, in which human fetal developmental patterns are closely approximated. They believe that their findings in these studies may have important implications for human fetal development.

According to the investigators, a human fetus develops the swallowing reflex early in gestation. By the time it approaches term, as much as 500 milliliters (or nearly one-half of the total amniotic fluid) is cycled through the fetus in a 24-hour period. Thus, they explain, it may be possible to provide nutrients to the fetus via the amniotic route in cases of maternal nutritional deficiency or to administer drugs to remedy various fetal disorders. They speculate that it may also be possible to inject antigens into the amniotic fluid in order to trigger a prenatal immune response. This route may be preferable to the transplacental pathway because some macromolecular compounds do not cross the placenta.

Drs. Orlic and Lev presented the results of their studies at the Federation of American Societies for Experimental Biology meeting in Atlantic City, April 19, 1973.

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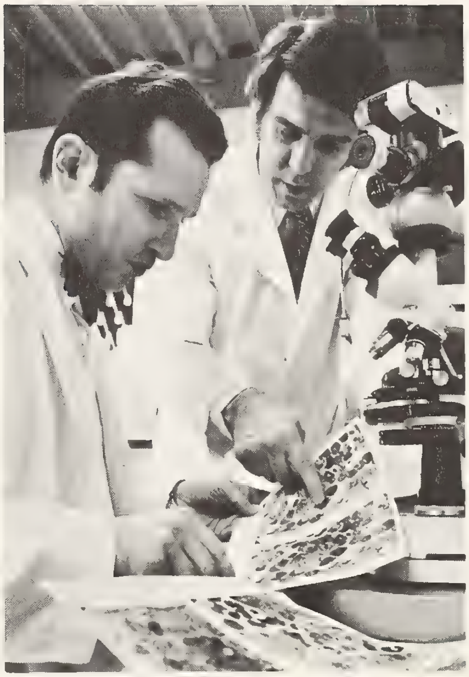
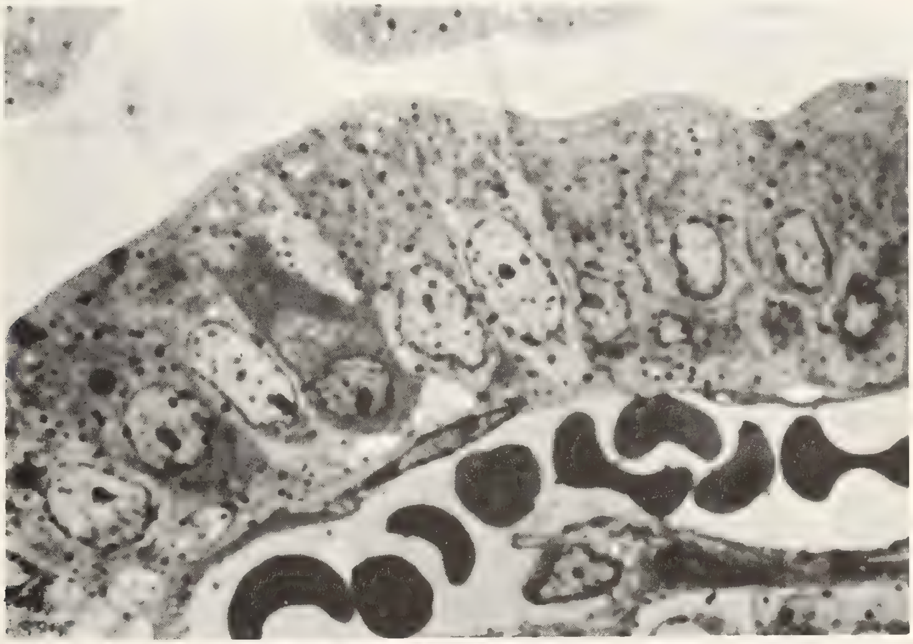
Amniotic Fluid (Cont'd)



Drs. Robert Lev and Donald Orlic check radioautographs demonstrating their findings in studies of fetal absorption of iron from swallowed amniotic fluid in the rat. (NIH Photo #1062). Below, a radioautograph shows this absorption by the mucosal epithelium of the fetal intestine in the rat. The silver grains (black dots) over the cytoplasm indicate passage of radioiron through the cell to underlying connective tissue and blood vessels. Within the blood vessels, several circulating red cells also demonstrate radioiron incorporation. (NIH Photo #1063)



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Research Advances

RESEARCHER DETECTS ENZYME IN CELLS WHICH DIGESTS DOUBLE-STRANDED RNA

National Institute of Dental Research (NIDR) scientists have detected an enzyme in normal animal cells which digests an unusual RNA structure called double-stranded RNA. Most RNA (ribonucleic acid) serves as a code or template for the manufacture of proteins or serves as part of the protein-synthesizing machinery. Double-stranded RNA is thought to occur in cells only after virus infection.

According to NIDR researcher Robert Stern, M.D., and associate Joseph Wilczek, finding such an activity in normal cells raises several questions.

Dr. Stern is primarily interested in learning why a normal, presumably uninfected cell should be armed with a specific tool for ridding itself of materials it comes in contact with only in the diseased state after a virus infection. And, he questions why a cell should have something aimed at an object it should never encounter normally.

Dr. Stern's research also suggests that perhaps there is no such thing as an uninfected cell. Perhaps all cells carry latent virus infections, some of which may be inherited. If so, the distinction between genetics and environment is an arbitrary one.

Another question puzzling the researcher is the possibility that it is incorrect to say that double-stranded RNA occurs only in the replicative cycle of RNA viruses. There is some indication, he explains, that small amounts of double-stranded RNA do exist in normal animal cells. This has escaped attention up to now because it is present in such small amounts.

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In his studies, Dr. Stern initially found the enzyme in serum, and then in wandering scavenger cells (macrophages) especially in the lung and the spleen. According to the investigator, the ribonuclease directed against double-stranded RNA is unusual in that it is made in neither the liver nor the pancreas, but rather in macrophages which are part of the reticuloendothelial (or RE) system of the body. (The RE system is the body's first line of defense against viral infection.)

Double-stranded RNA's are also potent inducers of interferon, Dr. Stern explains. Interferon, an antiviral substance made by the body, is also the reason why it is almost impossible to be infected with two viruses at the same time. This is one of the body's additional lines of defense against viral infection.

Now, synthetic double-stranded RNA's can be injected into the body and interferon will be produced. But the serum enzyme quickly destroys the double-stranded RNA, limiting the usefulness of synthetic interferon inducers. So, Dr. Stern suggests, the double-stranded ribonuclease may be part of a complex system of checks and balances in the body's fight against virus infection.

Another enzyme made in the pancreas, ribonuclease A (RNase A), is the chief enzyme for the digestion of RNA. Dr. Stern found it interesting to compare RNase A with the enzyme directed against double-stranded RNA. Assuming that the ribonuclease directed against double-stranded RNA is actually a mutant or modified form of ribonuclease A or that the two enzymes had a common ancestor long ago, the researcher set out to prove or disprove

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this hypothesis. Dr. Stern feels that the hypothesis is not totally arbitrary because both enzymes have the same "substrate specifity" and require the same material at the site of attack, a pyrimidine. However, while ribonuclease A requires only a pyrimidine, the ribonuclease directed against double-stranded RNA demands that the pyrimidine be in a base-paired, or spiral, configuration.

A comparison of the two enzymes showed Dr. Stern that the double-stranded ribonuclease is much larger when measured on a molecular sieve than ribonuclease A. Also, he found that there is a naturally occurring inhibitor in liver cells which inhibits ribonuclease A. It has no effect on double-stranded ribonuclease.

According to the researcher, the only way to prove or disprove his hypothesis is to work out an accurate, rapid, and sensitive assay for the purification of the enzyme. He is now at work toward that end. After purification, the large enzyme will also be a tool for examining the structure of viral RNA's.

It was recently shown that a particular RNA participates in the replication of DNA and of certain DNA tumor viruses. A double-stranded RNA occurs in the reading of the DNA late in the infection. One of the two strands of RNA or portions from each of the two strands must be digested away before the infectious process can continue. An enzyme similar to or identical to the one Dr. Stern detected may be involved in processing the two RNA strands.

Dr. Stern presented his findings at the Federation of American Societies for Experimental Biology meeting in Atlantic City, April 19, 1973.

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Research Advances

NEW PROCEDURE EXPLAINS HOW VACCINES PROTECT THE BODY

Scientists have shed new light on the way in which vaccines help protect the body against viral infections.

Russell W. Steele, M.D., of the Georgetown University School of Medicine, and colleagues have used a new procedure to test the effectiveness of rubella vaccine in infants. The study produced new knowledge on the working of the immune mechanism and helped explain why some people are devastated by viruses while others are not. The findings also help explain why premature babies are more susceptible to infection than full-term infants. The new method, developed by the Department of Pediatrics at Georgetown, "has wide application to studying any virus infection," according to Dr. Steele.

This study was supported by a grant from the National Institute of Child Health and Human Development to Joseph A. Bellanti, M.D., of the Georgetown University Department of Pediatrics and Microbiology. Dr. Steele, a fellow in immunology at the University, was joined in his work by David A. Fuccillo, Ph.D., of the National Institute of Neurological Diseases and Stroke.

In order to control viral disease, a vaccine must stimulate the entire immune system. (This system recognizes and attacks foreign invaders such as virus.) In effect, both aspects of immunity--the antibodies and the cell-mediated response (the action of white blood cells (lymphocytes) working to inactivate an invading virus)--must "turn on."

Traditionally, vaccines have been evaluated by measuring only antibody response. Recently, the cell-mediated response has been recognized as

(more)

equally important. However, no practical, accurate method of measurement had been developed. According to Dr. Steele, the new procedure is a breakthrough in evaluating and understanding vaccines.

The researchers developed a specific, practical method for measuring the cell-mediated response and used it to study infants vaccinated with live rubella virus. They found that the rubella vaccine proved effective in stimulating immunity.

In their study, the investigators immunized 12 children, aged 12 to 25 months. After immunizing the children, they drew a small amount of blood and separated out the lymphocytes. They also took lymphocytes from two unimmunized children for controls.

Using uninfected animal cells and those chronically infected with rubella virus for this research, the researchers labelled each cell with a radioisotope chromium 51. Then, they added the children's lymphocytes to the target cells and studied the interaction.

They interpreted the amount of chromium released when the lymphocytes destroyed or injured infected host cells as a measure of lymphocyte reaction. Then, the investigators subtracted the amount of chromium released from the controls from the amount released from the infected cells to get the net amount reflective of lymphocyte viral response. They did this separately for lymphocytes from the immunized and unimmunized children.

According to Dr. Steele, the procedure can be used to study prior immunity, to see if a vaccine "takes" and to identify individuals with defects in cell-mediated immunity. It can also be applied to studies of

(more)

transplant rejection and studies of immune response in cancer patients, of suspected "slow viruses" like multiple sclerosis, and of congenital nervous system diseases.

Using this procedure in their studies, the investigators report that for the first time they showed that cell-mediated response develops much faster than the specific antibody response. Cell-mediated immunity occurred three days after immunizations while antibody response took about 14 days. The sequence had been suspected but never previously shown.

Dr. Steele believes that these findings "go a long way in explaining why some people with adequate antibody reaction, either before or after immunization, still suffer devastating effects from viral infections--their cell-mediated response is not "turned on."

The Georgetown investigators also found that the immune response in premature infants was lower than in full-term children. This delayed immune competence may account partly for the known increased susceptibility of premature infants to infection, especially respiratory infections during the first two years of life.

According to Dr. Steele, in acute viral infections, the host cell is generally destroyed by invading virus which is then released and open to attack by an antibody. In "slow virus" infections or chronic infections such as congenital rubella, however, the virus may continue to live in the host cell until the lymphocytes go into action to destroy the host cell, releasing virus for antibody action.

(more)

Dr. Steele presented these findings at the Society for Pediatric Research meeting in San Francisco, May 19, 1973. His co-investigators were Dr. Fuccillo, Dr. Bellanti, and Sally A. Hensen and Monroe M. Vincent of Microbiological Associates, Bethesda.

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Photo Feature

RESEARCHERS USE TELEVISION IN AIDING STROKE PATIENTS

Manfred J. Meier, Ph.D., director of the neuropsychology laboratory at the University of Minnesota Medical School, has developed a unique method of using television to help victims of stroke. Stroke patients try to place wooden blocks into slots while viewing their actions on a television screen. The investigator may vary the task by reversing or inverting the television image. Evaluation of the patient's performance under these different conditions can help pinpoint where a stroke has caused damage in the brain.

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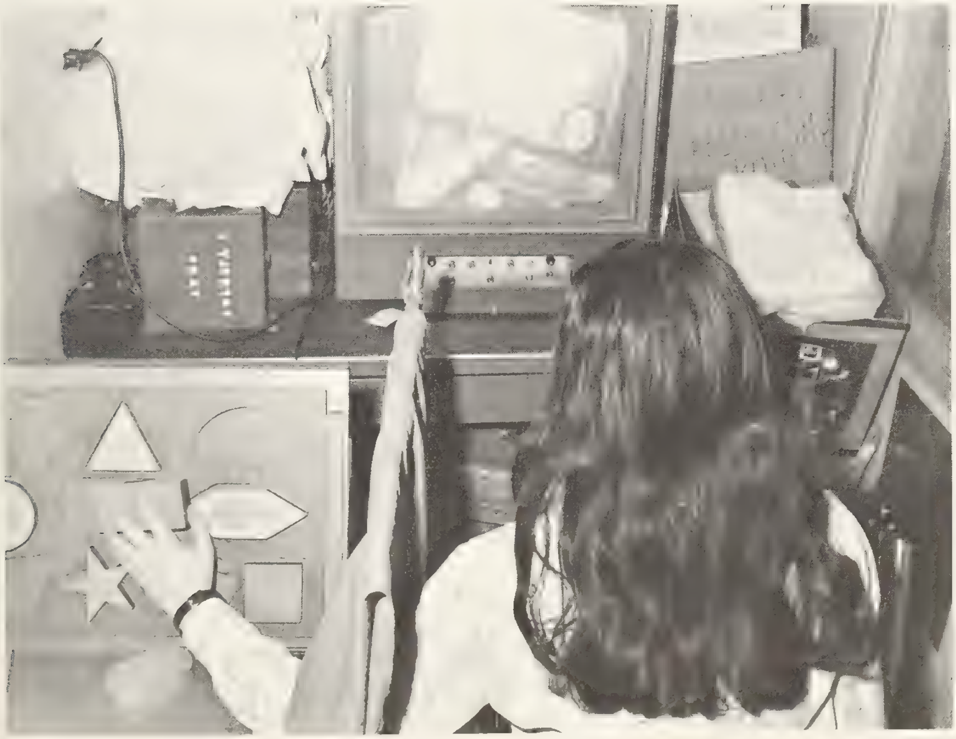

A stroke victim attempts to put blocks into slots while watching her actions on a television screen. This method of using television to help stroke patients was developed by Dr. Manfred J. Meier, a NINDS grantee at the University of Minnesota. (NIH Photo #1064)

Television (Cont'd)

Robert Thomas, Ph.D., a neuropsychologist at the University, administers the tests. He explains that some stroke victims experience conflicts between motor and visual information, which are due to damage in the posterior portion of the brain and which often go unnoticed. Although such problems are subtle, they can cause disorientation and make rehabilitation difficult. The TV test helps the physician catch these small problems.

In addition to helping researchers localize the brain damage, the test gives them an idea of the extent of the damage, and helps them predict which functions the patient may recover.

Dr. Meier's work is funded by the National Institute of Neurological Diseases and Stroke (NINDS). His test, which also has applications in localizing brain damage due to other causes, was developed and first used at the University of Minnesota. It is now being used in stroke centers throughout the country and in other countries.

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NOTE TO SCIENCE WRITERS: The NINDS-supported Stroke Research Centers will be featured in a future NIH Portfolio.

Photo Feature

In Wisconsin...

BIOTRON SCIENTISTS CHECK INFLUENCE OF ENVIRONMENT

The Biotron facility at the University of Wisconsin, Madison, makes it possible for scientists trained in many different disciplines to study some of the fundamental ways in which both healthy and diseased organisms respond to the world around them, according to Harold A. Senn, Ph.D., Biotron Director.

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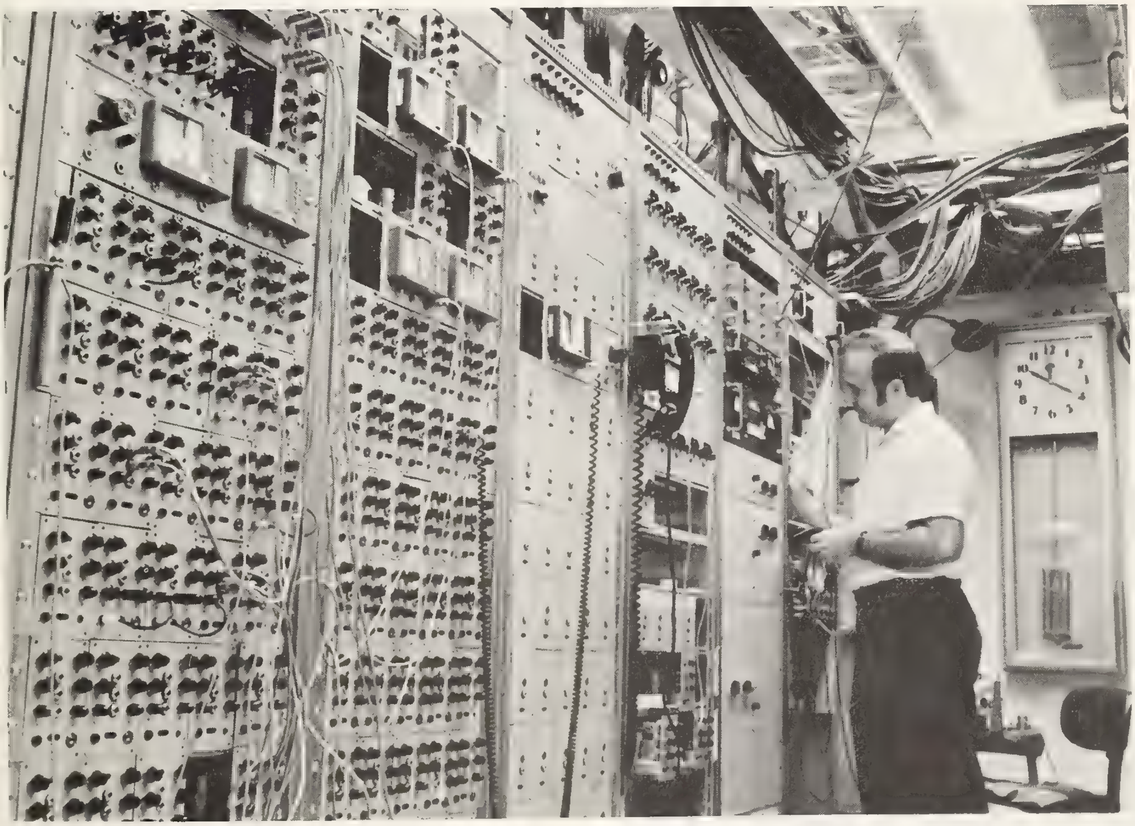

The Biotron's "foreman," a computer, is examined by Biotron staff member James Sumrall. The clock in the background keeps precise time to 1/1000 second. Biotron is located at the University of Wisconsin. (NIH Photo #1065)

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Biotron (Cont'd)

Biotron was built in 1962 with the aid of National Institutes of Health funds, and certain projects now receive support from the NIH Division of Research Resources through its General Research Support program.

A vital part of Biotron is the power plant where special pipes carry various agents that heat or cool the many experimental rooms. A computer is programmed to hold environmental factors constant or to modify them at ten-minute intervals in order to provide cycles of daily and seasonal change during the experiments.

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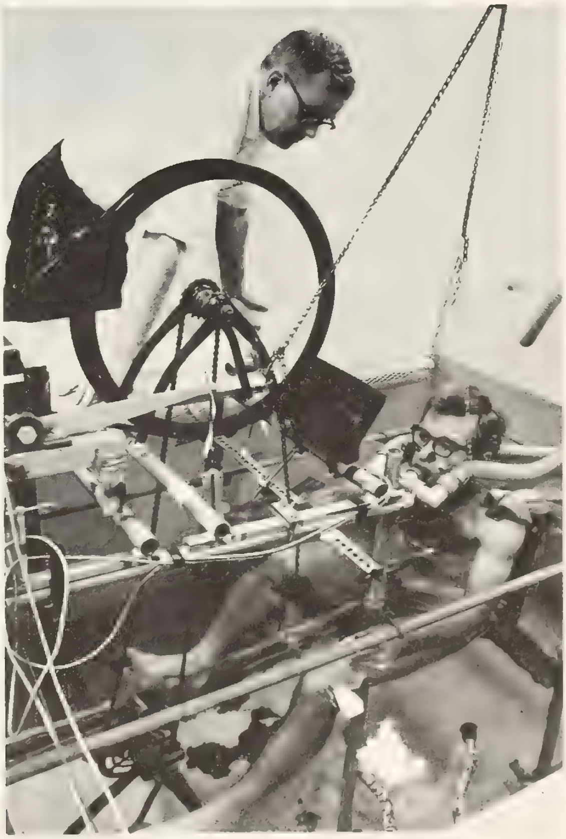

William Reddan, Ph.D., pedals his ergometer, a machine which measures muscular energy output. He is studying the effect of underwater exertion on circulation in the heart and lungs. Biotron Assistant Director Larry Anderson looks on. (NIH Photo #1066)

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Biotron (Cont'd)

Biotron's Wesley Clayton tests rat response to concentrations and aerosol propellant substances responsible for Sudden Sniffing Death (SSD). SSD involves "turning on" by inhaling large amounts of aerosol products. (NIH Photo #1067)

COVER PHOTO: Honey bees need a very specific environment at all times. Biotron Assistant Director Cal DeWitt observes honey bee respiration. (NIH Photo #1068)

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Photo Feature

HEW SECRETARY WEINBERGER WELCOMES NEW NIH DIRECTOR

Caspar W. Weinberger, Secretary of Health, Education, and Welfare, has welcomed the appointment of Robert S. Stone, M.D. as Director of the National Institutes of Health.

Secretary Weinberger said, "The National Institutes of Health has a justly famed tradition of excellence. In Dr. Stone, we have a man who will carry on that tradition, and who at the same time has the experience and maturity to lead the NIH through the challenging days ahead. We are fortunate in having a man of his caliber in such a key spot on our new health team."

Secretary Weinberger said Dr. Stone, who has been vice president for health sciences and dean of the School of Medicine at the University of New Mexico, Albuquerque, has already begun his NIH duties.

Dr. Stone, 51, has been dean since 1968 and served as associate dean for two years prior to that. As vice president, he coordinated the University's programs in medicine, pharmacy, and nursing, the New Mexico Regional Medical Program, and the Bernalillo County Medical Center.

For the past year Dr. Stone has been on leave from the University, acting as visiting professor at the Sloan School of Management, Massachusetts Institute of Technology. In this position he has been concerned with the use of modern systems of engineering and administration to integrate activities into a comprehensive health care operation.

Dr. Stone joined the University of New Mexico faculty in 1963 as professor and chairman of the pathology department. He previously was a member

(more)

Dr. Stone (Cont'd)

of the pathology department at the University of California at Los Angeles (UCLA) School of Medicine for 11 years. From 1957-59 he was deputy coroner at Los Angeles County and for several years was pathologist for the Los Angeles Shriner's Hospital for Crippled Children.

In 1959-60 he served as Chief of Research in Pathology for the Atomic Bomb Casualty Commission, Hiroshima, Japan. As a result of this work and continuing interest, he was named a member of the Advisory Committee to the Atomic Bomb Casualty Commission of the National Academy of Sciences.

Dr. Stone was born in New York City and educated at Brooklyn College and the State University of New York College of Medicine, Brooklyn. He was instructor in pathology at Columbia University College of Physicians and Surgeons before moving to UCLA.

His research appointments have included: Associate Investigator, Department of the Army Contracts, 1958 and 1960; Investigator, U.S. Public Health Service grant for tumor-virus studies, 1960-64; Co-Investigator, Veterans Administration research grant on lung diseases, 1964-68; Principal Investigator, American Cancer Society grant for research on viral cancers, 1955-56; and Principal Investigator, National Cancer Institute, NIH, for meson radiotherapy of cancer, 1970-72.

Dr. Stone is a member of the Executive Council, Association of American Medical Colleges. He is on the editorial board of the *Journal of Medical Education*, and is managing editor of the medico-legal journal *Trauma*. He is a member of Alpha Omega Alpha, medical honor fraternity.

(more)

Dr. Stone (Cont'd)

Robert S. Stone, M.D.
Director,
National Institutes of Health
(NIH Photo #1069, 1070, 1071, 1072, clockwise, from top left)

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NEWS & FEATURES From NIH June 10, 1973

Photo Feature

NIAID ADDS FOUR ASTHMA AND ALLERGIC DISEASE CENTERS

The National Institute of Allergy and Infectious Diseases (NIAID) has funded four more Asthma and Allergic Disease Centers.

The network of Centers now totals 14 in 11 states. "These outpatient-oriented centers," according to NIAID Director Dorland J. Davis, M.D., "appear to provide the best mechanisms for shortening the time lag between laboratory findings and the practice of clinical allergy."

The new Centers are Louisiana State University, New Orleans; Mayo Foundation, Rochester, Minnesota; Northwestern University, Chicago; and University of California at San Francisco.

Investigators at Louisiana State University School of Medicine, led by John E. Salvaggio, M.D., professor of medicine and microbiology, will study hypersensitivity lung diseases. These conditions, resulting from exposure to a variety of inhaled substances, cause shortness of breath and weight loss. The group's studies will be concerned with both experimental animal models and affected patients. By identifying and characterizing some of the causative substances, known as antigens, they hope to learn more about the underlying mechanisms involved in the disease.

Gerald J. Gleich, M.D., assistant professor of microbiology and internal medicine at the Mayo Foundation's Graduate School of Medicine, will head a group interested in two fundamental aspects of inflammation accompanying allergic reactions. They will try to define the functions of the eosinophil, a characteristic type of white blood cell which accumulates in abnormally

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large numbers in the blood and tissues of allergic individuals. The group will also study immunoglobulin E (IgE), one class of antibody or blood protein important in allergic reactions.

The Center to be directed by Roy Patterson, M.D., professor of medicine at Northwestern University Medical School, will focus on the diagnosis and treatment of allergic diseases involving the respiratory tract and skin. New methods of diagnosing immediate-types of hypersensitivity states and improved procedures of immunotherapy for asthma will be evaluated. They will also investigate the relationship of IgE with atopic eczema and chronic urticaria (hives) and the possible connection between respiratory allergies involving IgE and glomerulonephritis, a kidney disease.

The fourth Center, located at the University of California School of Medicine in San Francisco, will be headed by Oscar L. Frick, M.D., professor of pediatrics. Under investigation will be the causative and associated factors involved in the development of allergic diseases in infants and children. These will include genetic and environmental factors, as well as the interplay between them.

The Asthma and Allergic Disease Center Program was established by NIAID in 1971, in an effort to provide the means for developing improved diagnosis, treatment, and prevention of allergic disorders. The ten Centers already in operation are: Robert B. Brigham Hospital and Harvard Medical School, Boston, Massachusetts; Johns Hopkins University, Baltimore, Maryland; Washington University, St. Louis, Missouri; University of Wisconsin, Madison; Scripps Clinic and Research Foundation, LaJolla, California; University of

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Michigan, Ann Arbor; State University of New York, Buffalo; Children's Asthma Research Institute and Hospital and the National Jewish Hospital and Research Center, both in Denver, Colorado; and in the NIH Clinical Center at Bethesda.

Programs at these Centers involve studies of allergic individuals primarily on an outpatient basis. The NIAID Center involves an intramural research program. The other facilities are supported by NIAID research grants. Some of the subjects under study include the role of respiratory infections in asthma, improved methods of treatment for asthma and other allergic disorders, various forms of urticaria (hives) including angioedema (giant extensive tissue swellings), immunologic factors involved in allergic diseases, and related inflammatory reactions.

NOTE TO SUBSCRIBERS: The first ten Centers are featured in the *"NIH Portfolio on Asthma and Allergic Disease Centers*--April 1973."

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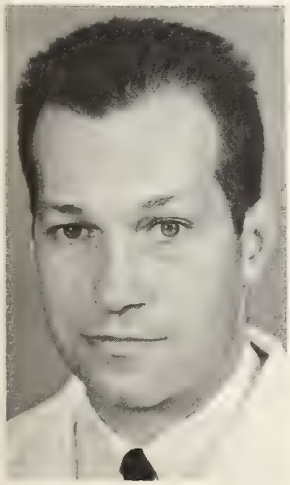
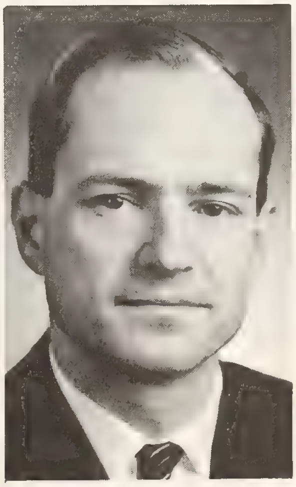


Dr. Salvaggio



Dr. Gleich

Dr. Patterson

Dr. Frick

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Medical News Tip

JUVENILE RHEUMATOID ARTHRITIS IN ADULTS--Rheumatoid arthritis in many respects is similar in the way it affects children and adults, but there are certain differences. Among these differences are frequent occurrences in children of high fever, skin rash, growth disturbances, other systemic and visceral manifestations, and the fact that rheumatoid factor is not frequently found in children's blood.

A 15-year-study by the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) of patients more than 16 years of age who have juvenile rheumatoid arthritis has suggested that this distinct disease entity may have its onset in adult life as well. All 15 patients fit into the disease onset pattern previously described for children, and the investigators have proposed that arbitrary age limits should not prevent recognition of so-called juvenile rheumatoid arthritis in adults.

The investigators concluded that juvenile rheumatoid arthritis can begin in adult life and that such patients may constitute a portion of adult subjects usually labelled "seronegative rheumatoid arthritis." Recognition and differentiation of juvenile rheumatoid arthritis in adult life is important because of the known brighter prognosis in cases of juvenile rheumatoid arthritis. All 15 patients responded to drug therapy.

For additional information, contact:

NIAMDD Information Office
Building 31, Room 9A-04
NIH, Bethesda, MD 20014
Phone (301) 496-3583

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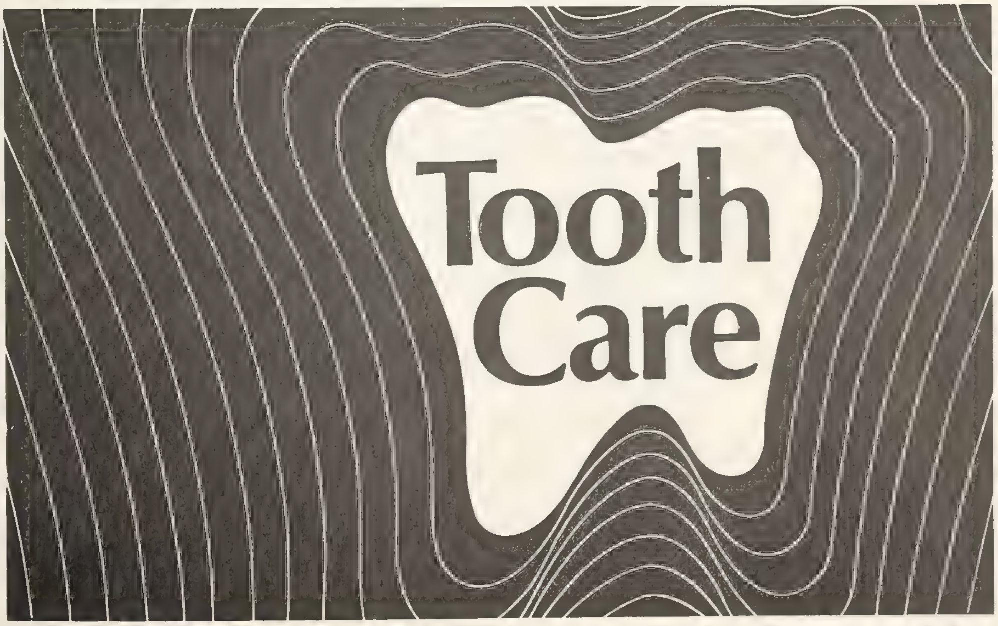
New Publication:
Tooth Care

Tooth Care, the first in a new HEW Consumer Information Series on the use of products and services relating to health, safety, and education, is sponsored jointly by the Division of Dental Health and the National Institute of Dental Research. The HEW Office for Consumer Services coordinated the booklet with the cooperation of experts in government, business, professional, and consumer groups.

This informative new publication is designed to aid an individual in maintaining healthy teeth and gums and in obtaining professional dental care. It contains home care procedures, as well as information on prevention and treatment of oral disease.

Science writers can obtain a copy of this booklet from:

National Institute of Dental Research
Building 31, Room 2C-33
National Institutes of Health
Bethesda, MD 20014
Phone: (301) 496-4261



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News Releases Issued

(Summaries of NIH releases sent out since the last issue. For a copy of any of these, please write or call.)

ENVIRONMENTAL HEALTH--HEW Secretary Caspar W. Weinberger announced on May 30 that the National Institute of Environmental Health Sciences (NIEHS) will provide approximately $2.9 million in grant funds over the next five years to the Mount Sinai School of Medicine of the City University of New York toward the establishment of a University-based Environmental Health Sciences Research Center. The new Center will be headed by Irving J. Selikoff, M.D., Professor of Community Medicine at Mount Sinai, who has been an NIEHS grantee for several years. With NIEHS support, Dr. Selikoff has brought together scientists with outstanding capabilities in epidemiology, biostatistics, chemistry, electron microscopy, and other disciplines necessary for sorting out factors that contribute to environmental diseases.

CANCER DATA--Launching of the first worldwide service to speed vital cancer information to physicians and scientists was announced by Frank J. Rauscher, Jr., Ph.D., Director of the National Cancer Institute (NCI). The NCI has awarded a $780,000 contract to Informatics, Inc. of Canoga Park, California, to develop the first phase of the Cancer Information Service (CIS). The 15-month contract will include the most extensive study in history of worldwide cancer data services, the information needs of cancer scientists, and how information about cancer can be made more available throughout the scientific community.

News Releases Issued (Cont'd)

GENETICS CENTER--The Yale University Medical School will establish a new Center for Human Genetics and Inherited Disease. The grant funds will total $364,712 in the first year, with expectation that the support will continue for five years. The Yale center is the eighth to receive support from the National Institute of General Medical Sciences under a program begun in June 1972 to accelerate research on the widespread problem of heritable diseases. According to medical authorities, genetic birth defects seriously afflict one in every 200 newborn children and are responsible for 40 percent of all infant mortality in the United States.

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June 25, 1973

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NEWS & FEATURES From NIH June 25, 1973

Research Advances

AEROSOL TB VACCINE PROTECTS MONKEYS

Evidence is mounting that aerosol vaccination against tuberculosis is a more effective method of preventing the disease than intradermal vaccination, the method most widely used today.

Latest research indicating this is so comes from a team of scientists at Hazleton Laboratories in Falls Church, Virginia, and the Tuberculosis Panel of the U.S.-Japan Cooperative Medical Science Program. The research was supported by a contract administered by the National Institute of Allergy and Infectious Diseases.

The team studied rhesus monkeys which had been vaccinated with the tuberculosis vaccine Bacillus Calmette-Guerin (BCG) in one of three ways--by aerosol, intravenously, or intradermally. A control group received no vaccine. The researchers chose rhesus monkeys because the animals get tuberculosis that closely resembles the human disease.

Eight weeks after vaccination the monkeys were challenged with small doses of virulent tuberculosis bacteria by an aerosol route. The experimental conditions thus simulated the spread of infection in man.

The researchers found that monkeys vaccinated by the aerosol and intravenous routes had fewer signs of disease than those receiving intradermal vaccination or those who were not vaccinated. Aerosol vaccination did not cause any adverse side effects. In contrast, all the monkeys vaccinated intradermally developed local draining abscesses around the vaccination site. Draining abscesses also occur in humans vaccinated intradermally. According

(more)

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to the investigators, intravenous BCG vaccination was as effective as the aerosol method but would be impractical for mass vaccinations in humans.

Mass vaccination against tuberculosis is used in most developing and developed countries. In one recent year, nearly 31 million vaccinations were given in 38 African and Asian countries, mostly by the intradermal method.

In the U.S., tuberculosis is no longer considered a major health problem and BCG vaccination is used only infrequently. However, the disease shows signs of increasing in some major American cities, and many public health officials have recommended that BCG vaccination might be used in specific high-risk populations.

Aerosol vaccination would lend itself readily to mass vaccination programs. A moveable console has been proposed that would automatically aerosolize the vaccine in a given room for a set time, take air samples, and wash out the residual bacteria. The unit could be moved from room to room and vaccination could be performed without disturbing the occupants. This is a highly effective route for immunization. It is painless, time-saving when done en masse, and psychologically more acceptable to the participants.

This study was reported in the March 1973 issue of *American Review of Respiratory Disease* by William R. Barclay, M.D.; William M. Busey, Ph.D., D.V.M.; Dan W. Dalgard, D.V.M.; Robert C. Good, Ph.D.; Bernard W. Janicki, Ph.D.; John E. Kasik, M.D.; Edgar Ribi, Ph.D.; Charles E. Ulrich, and Emanuel Wolinsky, M.D.

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Research Advances

NOISE FROM INCUBATORS MAY CONTRIBUTE TO DEAFNESS

Scientists suggest that incubator noise may contribute to the cause of deafness. According to the investigators, damage-risk criteria need to be established in infants and incubators must be designed in accordance with these criteria.

Stephen A. Falk, M.D., of the National Institute of Environmental Health Sciences, and Joseph C. Farmer, Jr., M.D., of the Duke University Medical Center, recently analyzed the noise from functioning infant incubators in an attempt to focus attention on noise as a possible factor in hearing loss.

The investigators measured six incubators, analyzing each twice by placing the sound level meter in the long axis of the incubator so that measurements were made with the microphone in two positions: where the infant's head would normally rest and at the infant's feet. Background noise for each incubator was measured with the incubator not functioning and compared with noise levels obtained with the incubator in a normally functioning mode.

Their study revealed an average noise level of 57.7 decibels (A-weighted) and 74.5 decibels (linear). The investigators found no difference in sound pressure levels when measured with the microphone placed in either position. Also, because of the masking effects of the incubator noise, the background noise level was insignificant in terms of damage risk. They found the sources of the noise to be the electric motor and fan below the infant compartment of the incubator.

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Noise as a cause of sensorineural hearing loss is well established in the otologic literature as are damage-risk criteria to prevent noise-induced permanent hearing loss. In adults, approximately 80 decibels is the maximal sound intensity unable to produce sensorineural hearing loss regardless of duration. According to previous investigations, approximately 89 decibels would be the highest allowable intensity.

Following these criteria, the 57.7 decibels and 74.5 decibels of noise seen in the present study would not be considered a potential risk to hearing. However, the investigators caution that several considerations should lead to a reevaluation of this conclusion.

First, the investigators explain that the present criteria are not applicable to noise exposure in infants because these criteria were established on studies of adult humans. To their knowledge, there have been no controlled studies concerning the effect of noise on young or newborn mammalian cochleas. They explain that until such knowledge is obtained, damage-risk criteria for this group cannot be established with certainty.

Additionally, Drs. Falk and Farmer note that the Subcommittee on Noise of the Committee on Conservation of Hearing has shown that continuous noise is more damaging than intermittent sound, which provides an opportunity for recovery. Damage-risk criteria established in adults are based on eight-hour-per-day exposures. Therefore, a premature infant, confined to an incubator for continuous periods of weeks or months, may be thus put to additional risk.

Furthermore, the investigators point out that a number of studies have demonstrated a potentiation of hair cell damage in guinea pigs following

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exposure to noise and ototoxic antibiotics simultaneously as compared to exposure to either agent alone. The scientists suggest that the use of potentially ototoxic antibiotics in the newborn who is constantly exposed to incubator noise is an analogous situation and should be considered in newborn and premature infant care.

Drs. Falk and Farmer report their findings in *Archives of Otolaryngology*, May 1973.

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Research Advances

Study in New England...

POLIO STILL POSES THREAT TO HEALTH

Just 20 years ago, most parents approached the summer season with dread, wondering if their child would be one of the many victims of polio. Today, the incidence of polio has dropped to an all time low, largely as a result of the massive oral poliovirus vaccination campaigns of the 1960s.

The very success of the polio vaccination campaign raises the question of whether equally serious central nervous system (CNS) infections--caused by enteroviruses other than polioviruses--would increase. Some public health officials suggested that the coxsackie viruses and echoviruses, which can cause aseptic meningitis and other CNS diseases, might rush into a community to fill the vacuum left by the departing polioviruses.

This fear likely can be laid to rest as a result of studies carried out by Dorothy M. Horstmann, M.D., and colleagues at the Yale University School of Medicine, New Haven. In a seven year survey of enteroviruses in two New England towns, the scientists found that continuous use of oral poliovirus vaccine did not result in an increase in the number or severity of other enterovirus infections. The investigation was supported entirely by the National Institute of Allergy and Infectious Diseases.

Dr. Horstmann and associates arrived at this conclusion by sampling sewage systems for viruses in Middletown and Portland, Connecticut. Sewage specimens collected at weekly intervals between 1961 and 1968 revealed the presence of polioviruses--mostly of the attenuated vaccine strain--regularly

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throughout the year with no seasonal variation. Other enteroviruses--coxsackies and echoviruses--were recovered mainly in the summer and autumn. (This is the usual pattern for these viruses.) They found no evidence that CNS infections associated with those enteroviruses were more frequent or more serious than they were prior to 1960, when oral polio vaccination was unknown.

The researchers also collected rectal samples from healthy infants and preschool children living in these towns and studied them for viruses. They found that over the same period, as many as seven percent of the children who were not vaccinated excreted polioviruses of the vaccine strain--presumably as a result of contact infection acquired from children who had been vaccinated. The scientists conclude that dissemination of the vaccine strains through contact infection probably contributes to raising the level of "herd immunity" among young susceptible children. (Herd immunity refers to the resistance of a group to attack by a disease to which a large proportion of the members are immune, thus lessening the probability that a patient with the disease will come into contact with a susceptible individual.)

Although most polioviruses isolated from both sewage and children were of the vaccine strain, the researchers also recovered wild type polioviruses from the sewage. This emphasizes the need for continued diligent use of oral vaccine to protect people from polioviruses still present in the environment.

In 1954, before the advent of the Salk vaccine, there were 18,000 cases of paralytic polio in the United States. In 1972 there were only 20 cases of paralytic polio, and, so far this year, only one case has been reported to

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the Center for Disease Control (CDC) in Atlanta. Because of this dramatic decline, many CDC officials fear that complacency toward vaccination has set in. In 1972 only 63 percent of the children between the ages of one and four received adequate vaccination against polio, a drop of four percent from 1971. The problem is most severe in the poverty areas of the major cities, where as many as half of the children are without protection, despite the fact that polio viruses are still present and are a potential threat to health.

The investigators published a report of their findings in the *American Journal of Epidemiology*, March 1973.

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Photo Feature

PRESIDENT NIXON MEETS WITH NEW NIH DIRECTOR

President Richard M. Nixon met recently in the Oval Office of the White House with the newly-appointed NIH Director, Robert S. Stone, M.D. (center). Also attending this meeting were HEW Secretary Caspar W. Weinberger (second from left), HEW Assistant Secretary for Health Charles C. Edwards, M.D. (fourth from left), and Associate Director of the Domestic Council James H. Cavanaugh, Ph.D. (NIH Photo #1073)

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NOTE TO SCIENCE WRITERS:

The following is a portion of a recent interview with Robert S. Stone, M.D., the newly-appointed Director of the National Institutes of Health.

Question: What do you believe to be the responsibility inherent in the title "Director of the National Institutes of Health"?

Dr. Stone: I feel extremely humble about this responsibility. It's a responsibility that is enormous in national terms and even international terms.

I view the Director's functions as a linking function. I would not put much emphasis on the word "director" as an operational word or in "directing" a great deal. That linkage role is vital to the continued good health of the Institutes. It is important that this role be carried out competently.

Question: What about the mission of the nation's major health research agency?

Dr. Stone: Obviously the NIH has been highly successful in its mission and it has a sustaining life of its own. What I hope to do is to facilitate an understanding of the mission, the needs, and the role of NIH among those who see it from the outside--whether they see it in terms of grant support or contract support or in terms of their needs to administer and be responsible for public funds.

I hope I will be able to strengthen the research function inherent in NIH activity and tradition.

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The creativity is here among the scientists. That has to be built upon. We have to make sure that it finds its full expression.

Similarly, we need to be sensitive to the fragility of the creativity of those who may be supported by NIH, through either grants or contracts.

Question: Would you please elaborate about the "creativity"?

Dr. Stone: Creativity is a part of scientific endeavor, whether the initiative arises exclusively from the investigator, or whether he becomes a collaborator as a part of some larger plan. In either case, his brightness, his quickness, his thoughtfulness, his ability to bring together diverse pieces of information to make a unified whole, must be fostered.

Question: Are there certain research areas that are of special interest to you personally?

Dr. Stone: My research interests of the past have included ultrastructure pathology, tumor-virus relationships, etiological synergisms in lung disease, the biological effects of atomic radiation, and meson radiotherapy of cancer. But I regard my present assignment as one of trying to be a multi-lingual interpreter, knowing that one is not really fluent in any one of the languages.

Question: What about the future?

Dr. Stone: For the future, I hope that NIH can foresee problem areas, so as to keep its momentum at a high level.

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I have been impressed with the way in which the top staff has an up-to-date inventory of existing problems and has been systematically working to solve them. For example, an intense study is now being made of the issue of research involving human subjects.

This is an example of the kind of process in which NIH is already extremely active. If we don't anticipate future changes in our turbulent environment, our ongoing work may falter. I would therefore put much emphasis on being far-sighted, to see where the mission of NIH is leading us and how it can be best fulfilled.

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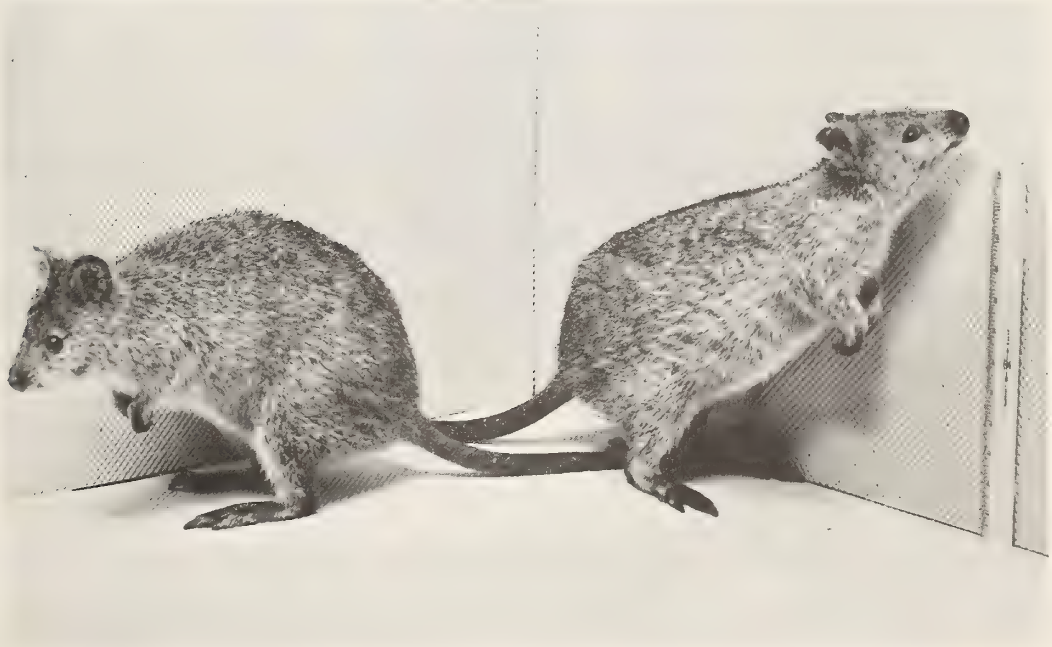
Photo Feature

AUSTRALIAN ROTTNEST QUOKKAS PARTICIPATE IN MUSCLE STUDY

Five Rottnest quokkas recently arrived in the United States to participate in a study of muscle diseases conducted by Shirley H. Bryant, M.D., at the University of Cincinnati Medical Center. The quokkas promise to provide significant information on such muscle diseases as myotonia, which causes weakness of muscles, and dystrophy, which results in muscle wasting and atrophy.

Quokkas are nocturnal wallabys, first cousins of the kangaroo but much smaller, being only about the size of a medium to large rabbit. The source of the name quokka is not known, but their abundance and their naked rat-like tail is the undoubtable source of the name Rottnest, their small island home about ten miles off the west coast of Australia.



Quokkas stand on their hind legs. They use their forelimbs a little when walking or hopping around slowly and bound along on their hind limbs over obstacles when disturbed. (NIH Photo #1074)

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Dr. Bryant became interested in the quokkas when he learned that they often develop progressive muscular weakness when fed a diet deficient in vitamin E. Also of great interest was the discovery that the condition could be completely reversed with a vitamin supplement.

The quokkas are the third animal species to participate in Dr. Bryant's muscle studies. The research colony was started in 1958 when a genetically controlled muscle disorder, myotonia, was identified in a registered strain of goats. Nicknamed "nervous," "fainting," or "stiff" goats, they demonstrated the inherited muscle fiber defect which permits repetitive production of muscle impulses. Thus, when a loud noise or unexpected movement startles these goats, they are literally "scared stiff," for their legs stiffen and they go down on their knees or fall to the ground.

The research program also includes certain highly prized pigeons, the "tumblers," which somersault backwards during flight, and the "rollers" which, though unable to fly at all, perform a series of as many as 30 backwards tumbles on the ground. Richard K. Entrikin, a graduate student working with Dr. Bryant, has found that these birds have neck muscles (biventer cervicis muscles) which stiffen and pull the head back. The muscles show abnormalities of electrical properties, fiber size, and response to drugs (especially acetylcholine).

To serve as comparison with animal studies, several dozen human volunteers in Cincinnati have donated muscle samples for this research. The investigator explains that neither the people nor the animals are harmed by the minor surgery performed under anesthesia.

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Quokkas (Cont'd)

The voltage clamp, recently adopted for muscle research by R.H. Adrian, M.D., University of Cambridge, England, will be used in the quokka studies. Small samples of muscle tissue are held by the voltage clamp in which three microelectrodes penetrate each fiber to measure the electrical currents of muscle cell membrane. Abnormal muscle contraction after a sudden movement appears to be a defect in the mechanism controlling the electrical currents of muscle cell membrane. It is believed that the voltage clamp technique will provide more intimate knowledge of differences in the membrane properties of myotonic and normal muscles.

These current animal studies are yielding much information about the electrical properties of both normal and abnormal muscle tissue. Such knowledge, the scientist feels, is the first step toward developing a cure or treatment for related human muscle defects. The quokka, goat, and pigeon studies all help explain a similar defect occurring in a human muscle disease known as Thomsen's disease (myotonia congenita) as well as in certain muscular dystrophies.

According to Dr. Bryant, "The increased understanding derived from these experiments may be useful in the design of better therapy or prevention of myotonia. It may also extend our basic knowledge regarding the nature of abnormal repetitive firing of excitable membranes--a phenomenon underlying two common human abnormalities, cardiac arrhythmias and epilepsy."

Drs. Bryant and Adrian plan to continue their collaboration on computerized muscle fiber models which should greatly increase research productivity. The computer can simulate the firing pattern of the abnormal muscle, thereby

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allowing the investigators to test their theories on the cause of myotonia. To facilitate the recording of muscle fiber activity, an experimental drug, dantrolene, is being used to calm the fibers and thus decreasing their mechanical movements.

Other facets of this research program include studies of neural factors and pharmacological and nutritional aspects (vitamin E) of mytonia. All should lead to a better understanding of the factors underlying normal and abnormal muscle physiology.

The work is jointly supported by the National Institute of Neurological Diseases and Stroke and the Muscular Dystrophy Associations of America, Inc.

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NEWS & FEATURES From NIH June 25, 1973

Photo Feature

NHLI GIVES STANFORD BIG HEART TRANSPLANT GRANT

A large grant for heart transplant research, totalling $2,500,000 over five years, has been awarded to Stanford University School of Medicine by the National Heart and Lung Institute.

"This award will enable us to continue to explore and evaluate the clinical application of heart transplantation," said Eugene Dong, Jr., M.D., principal investigator and associate professor of surgery at Stanford.

The primary goal of the research effort, Dr. Dong said, will be further refinement of the postoperative treatment of transplant patients. He said the program will focus on four main areas:

* improvement of the diagnosis of cardiac rejection
* development of new methods to treat rejection
* prevention of some of the long-term consequences of immunosuppressive drugs (drugs which check the body's immune or defense system)
* utilization of biomedical engineering to evaluate heart function in transplant patients

Rejection of the transplanted heart by the body's immune system remains the main obstacle to more successful heart transplantation. For years, researchers have sought better methods to detect and treat rejection in its earliest stages.

"We hope to determine the changes in the body's immune system which occur early in a rejection episode," Dr. Dong said. "If we can spot these changes before irreversible damage is done to the heart, we may be able to treat rejection more specifically and effectively."

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In addition to investigating new therapeutic drugs to combat rejection, the Stanford researchers plan to study more precisely how transplant patients respond to currently-used agents.

"We need to find out why two patients receiving the same drug treatment respond very differently, and why some patients require less drug therapy than others," Dr. Dong explained.

For long-term transplant survivors, one of the consequences of prolonged drug treatment has been the speeded-up development of atherosclerosis.

"We've noted in some of our early patients that there is a recurrence of the original heart disease in an accelerated fashion," Dr. Dong said. "Our current, still inconclusive data, indicate that through diet control, exercise, and anti-clotting drugs, this may be preventable."

Eugene Dong, Jr., M.D., associate professor of surgery at the Stanford University School of Medicine, checks some of the electronic equipment used to evaluate the clinical application of heart transplantation. Dr. Dong's work is supported by NHLI. (NIH Photo #1075)

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Grant (Cont'd)

The final area of research is related to evaluation of cardiac function in transplant patients.

"Unfortunately, many current methods of evaluation are invasive, with a small but definite degree of risk," according to Dr. Dong. "Our aim is to evaluate cardiac function using safe, non-invasive, non-painful, and non-toxic techniques."

These techniques include computerized analysis of electrocardiograms and echocardiograms (measurement of the heart's rate of motion, chamber size and wall thickness, using high frequency sound waves).

Co-investigators with Dr. Dong will be Norman E. Shumway, M.D., professor and head of the division of cardiovascular surgery; Edward B. Stinson, M.D., assistant professor of surgery, and John S. Schroeder, M.D., assistant professor of medicine.

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Photo Feature

Following Heart Attack...

SCIENTISTS SEEK TO REPLACE SCAR TISSUE WITH NEW MUSCLE

University of Chicago scientists are seeking a method to regenerate damaged heart muscle tissue following a myocardial infarction.

When heart muscle (myocardium) is damaged because of a lack of blood supply--as occurs after occlusion of a coronary artery--part of the muscle may die (infarct). Surrounding areas may be damaged but still survive. In the adult human heart, dead cardiac muscle cells are replaced by scar tissue, not by new muscle. The normal adult cardiac muscle cell has apparently lost the ability to divide.

Murray Rabinowitz, M.D., Professor of Medicine and Biochemistry, Radovan Zak, Associate Professor of Medicine, and Donald Fischman, M.D., Associate Professor of Anatomy and Biology, of the University of Chicago, are conducting several basic studies of cardiac muscle cell injury, repair, death, and regeneration, which are supported in part by National Heart and Lung Institute (NHLI) funds.

Much of the work was performed in the University of Chicago Myocardial Infarction Research Unit (MIRU), one of nine MIRU's in this country supported by NHLI research contracts. In addition, Drs. Rabinowitz and Fischman receive NHLI research grant funds in support of their research.

In one study, the investigators expose experimental animals to low oxygen atmospheres to elucidate the susceptibility of different structures within the heart muscle cell to injury by hypoxia (deficiency of oxygen), and to examine the repair processes after reoxygenation.

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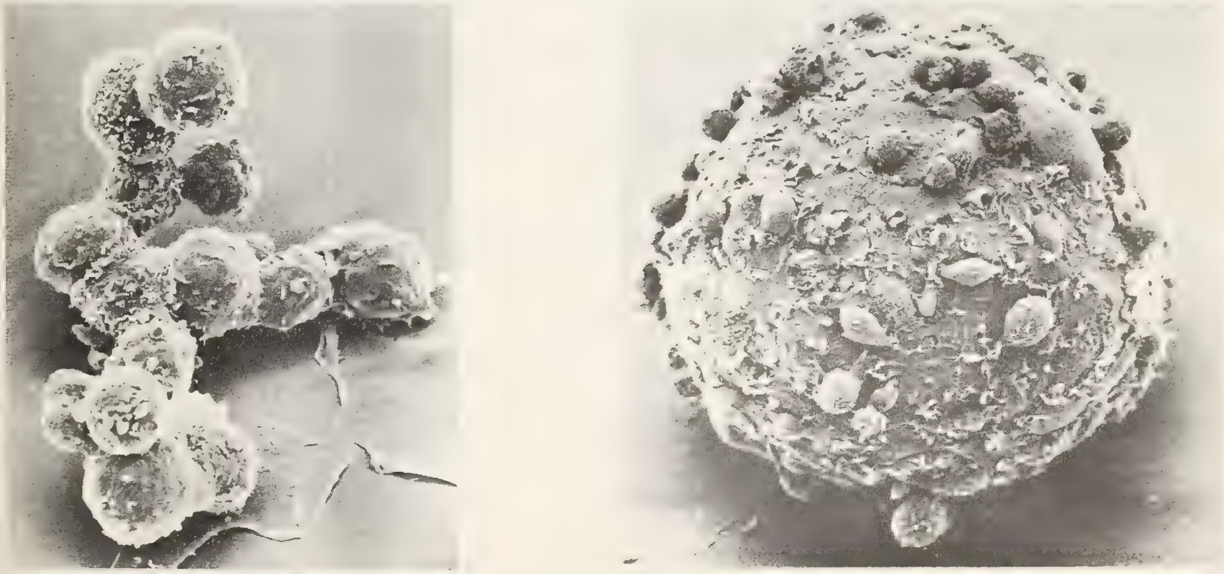
In another study, the scientists exercise experimental animals on a treadmill for prolonged periods. A severe circulatory burden is then imposed on the heart by constricting the animals' ascending aorta (the major artery conducting blood away from the heart). This overworks the heart by forcing it to develop a higher head of pressure to eject blood through the narrowed vessel. From this study, the investigators can evaluate possible physiological and biochemical advantages of such exercise conditioning in enabling the heart to cope with its added burden.

The research team is also seeking to determine factors which restrict cardiac muscle cell division in adults. It is of great practical importance to determine if adult heart muscle cells can be made to reinitiate cell division and to regenerate. In this way, the heart can possibly replace dead muscle with normal muscle rather than scar tissue. An intensive study



As seen in scanning electron micrographs from the University of Chicago, individual embryonic heart cells of chicks (left) are aggregating after two hours in the test tube. In the right photo, under smaller magnification, aggregation is almost completed after 12 hours and a spherical mass is observed. (NIH Photos #1076, 1077)

(more)

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of the development of cardiac muscle cells at varying ages--embryo, young, and adult--and in tissue culture is under way.

In order to better understand the relationship between intercellular contact, DNA synthesis, and myofibrillar assembly, the scientists are performing scanning and transmission electron microscope studies on the aggregation of dissociated, embryonic, chick, and mouse heart muscle cells in suspension culture. Yutaka Shimada, M.D., on leave from Chiba University, Japan, works with Dr. Fischman in electron microscope studies of heart muscle cells.

This reaggregated heart tissue, like normal heart tissue, contracts in the test tube. The individual cells can be observed joining together into tissue. The cells attach, forming new intercellular boundaries.

In still another research effort, the investigators are establishing methods for maintaining tissue cultures of adult rat heart cells. According to Dr. Fischman, "These studies have demonstrated that we can maintain adult heart cells in a contractile (functional) state for at least two weeks *in vitro*.

"Our studies suggest that mature heart cells, at least from rats, can be maintained in culture, but to our knowledge no one has yet attempted similar studies with human material. These culture systems will be used for studying DNA, RNA, and protein synthesis in cultured mature heart cells."

The underlying purpose of the research, according to Dr. Fischman, "is to clarify factors which prevent the regeneration of heart muscle cells after injury in the adult. Apparently, myocardial cells, after the neonatal (newborn) period, are incapable of cell division and DNA synthesis."

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NEWS & FEATURES From NIH June 25, 1973

Medical News Tip

SCIENTISTS STUDY CRIB DEATHS IN WASHINGTON--Results of a 44-month study of all sudden infant death syndrome (SIDS) cases occurring in King County, Washington, point to viral infections as playing a leading contributory role. This and similar recent epidemiological studies are providing a base upon which scientists may be able to build a theory to explain the causes of SIDS.

Out of 73,315 infants born during the study period, 170, or one in every 432 live births, died of SIDS.

University of Washington investigators, partially supported by the National Institute of Child Health and Human Development (NICHD), found seasonal clustering of SIDS and suggested this indicated that the syndrome has epidemic-like characteristics, and may implicate viral infections.

Other evidence included an increased incidence among male infants. Scientists found increased occurrence in low social class and in nonwhite families, among whom infections are believed to spread faster because of crowded living conditions. Moreover, 44 percent of SIDS babies had "colds" during the two-week period prior to death.

Abraham S. Bergman, M.D., and his associates believe that viruses probably act more as a "triggering agent" than as a cause.

For additional information, contact:

NICHD Information Office
Landow Bldg., Room A804
Bethesda, MD 20014
Phone (301) 496-5133

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New Publication:
Basic Data Relating to the NIH 1973

Academic institutions receive most of the Federal medical research money, according to statistics published in *Basic Data Relating to the National Institutes of Health 1973.*

Among the facts presented in the data book is that medical and health-related research, which represents only 11 percent of the nation's support of research and development programs, is characterized by a flow of public money to non-Federal, non-profit institutions. The Federal Government supports 63 percent of the Nation's medical research, but conducts only 17 percent.

Also included are facts about the NIH staff as of November 30, 1972. On the NIH professional staff there were 2,319 people with doctorate degrees including 127 with more than one doctorate.

Science writers can obtain a free copy of this publication from:

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News Releases Issued

(Summaries of NIH releases sent out since the last issue. For a copy of any of these, please write or call.)

TRAUMA--The National Institute of General Medical Sciences has awarded a trauma research grant to Denver General Hospital. Ben Eiseman, M.D., who will direct the research, explains that among the local injury problems are complications caused by lowered oxygen content in the blood of residents of the "mile high" city, problems of young people who are injured while under the influence of hallucinogenic and narcotic drugs, and the need for early detection of fat emboli that can lead to pulmonary embolism. The hospital handles more than 95 percent of all Denver area injury cases. Dr. Eiseman is Professor of Surgery at the University of Colorado School of Medicine.

ACUPUNCTURE GRANT--A three-year grant to the Missouri Institute of Psychiatry in St. Louis from the National Institute of General Medical Sciences begins Federal funding of research to assess the pain relieving capabilities of acupuncture. Physicians at the St. Louis facility, an affiliate of the University of Missouri School of Medicine, will compare the analgesic qualities of acupuncture anesthesia with those of standard pain-relieving drugs as well as hypno-anesthesia. Two groups of volunteers--a group suffering chronic and continuing pain, and a control group--have been recruited for the project. A major purpose of the project is to develop a better understanding of how the brain functions, particularly in response to anesthesia and pain as well as to learn more about acupuncture.

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